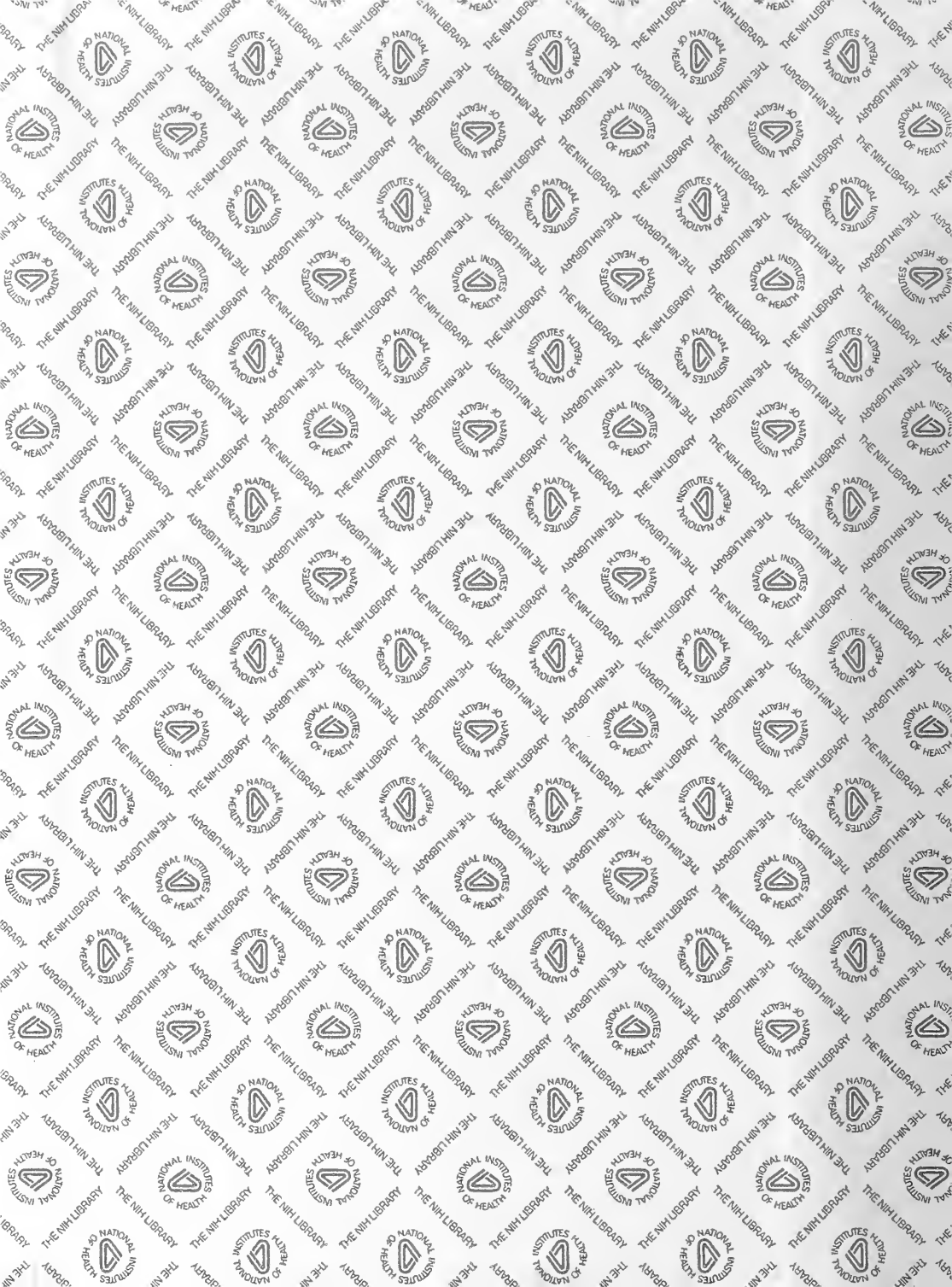
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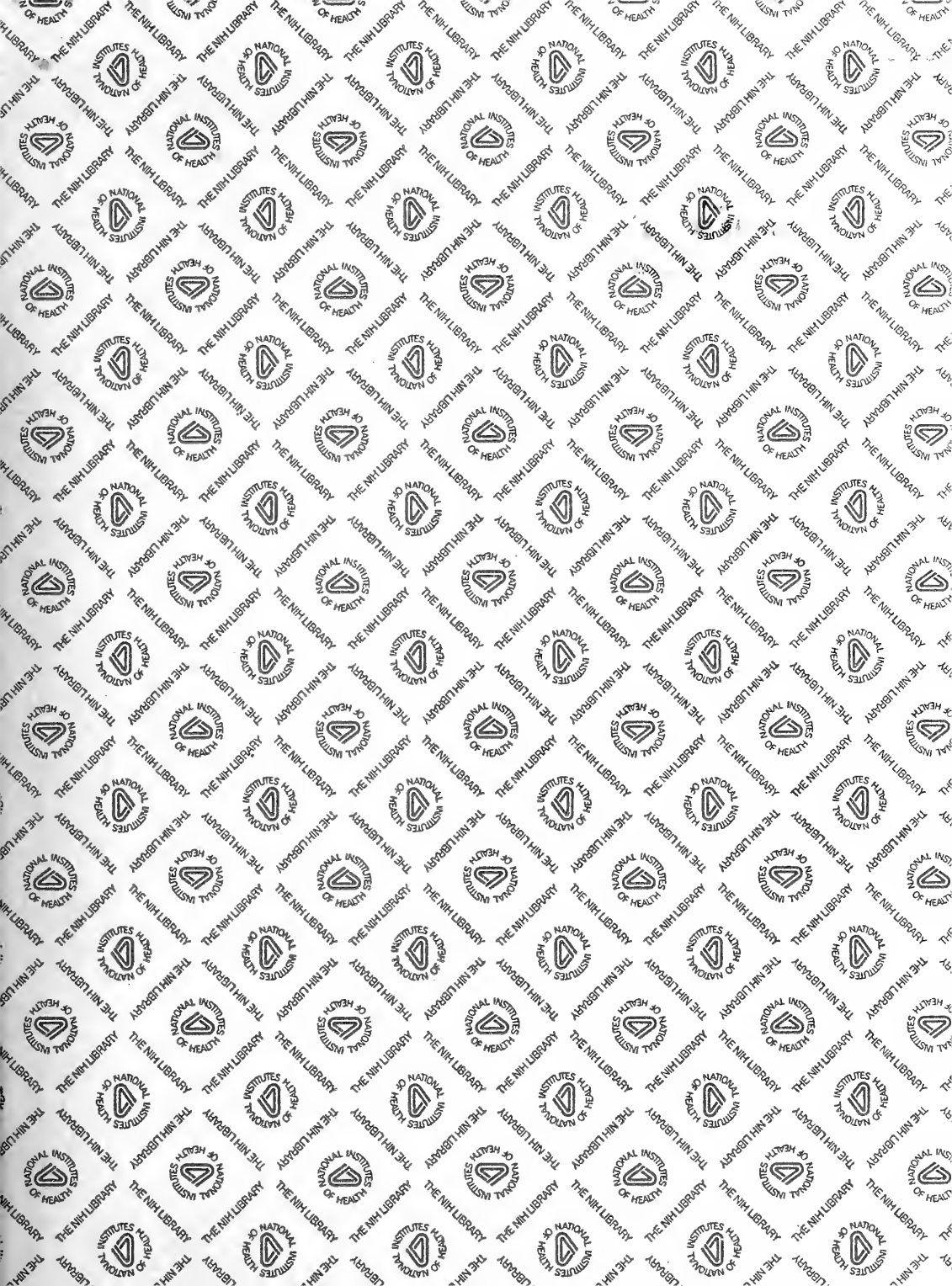
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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00001-10 BPGS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Control of Behavior by Drug Injection

PRINCIPAL INVESTIGATOR

P.I.	Steven Goldberg, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Christine Sannerud, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	Charles Schindler, Ph.D.	Research Psychologist	Preclinical Pharmacology Laboratory
	Charles Schuster, Ph.D.	Senior Scientist	Office of the Director
	Stephen Heishman, Ph.D.	Research Psychologist	Clinical Pharmacology Branch
	Jose Prada	Research Psychologist	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4.5	2	25

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Drugs serve as positive reinforcers to maintain and strengthen behavior leading to their administration and can control behavior through their ability to function as discriminative stimuli. In many situations, drugs of abuse function through pharmacological and behavioral mechanisms to persistently sustain long sequences of drug seeking behavior that are very resistant to extinction. These long sequences of drug-seeking behavior can be analyzed using schedule-controlled performances in the same way as operant behavior maintained by other events such as food or shock. Using a variety of intravenous self-administration procedures in rats and primates, ongoing experiments are being conducted to evaluate behavior maintained by drugs and the ability of pharmacological treatments, (i.e., antagonist administration or the development of dependence) and/or behavioral manipulations to modify drug self-administration behavior and/or food-maintained behavior. These studies will compare responding maintained under fixed-ratio, fixed interval and complex second-order schedules, by various drugs including cocaine, nicotine and other psychomotor stimulants, benzodiazepines and other sedative/anxiolytics, morphine and other opioids and delta-9 THC (the active ingredient of marijuana). For example, since serotonergic mechanisms appear to underlie psychomotor stimulant action, recent studies evaluated the effects of sertraline, a selective serotonergic uptake inhibitor that is effective as an antidepressant, on the reinforcing effects of i.v. nicotine in squirrel monkeys. In addition to differences in the pharmacological efficacy of drugs to control or modify behavior, it is clear that behavioral and environmental factors play an important role in the control that even highly efficacious drugs exert on behavior. The focus of experiments in the rhesus self-administration lab are to study the pharmacological, behavioral, and environmental variables involved in initiating and maintaining drug self-administration. Recent studies assessed rates of acquisition of cocaine self-injection in rhesus monkeys found a relationship with behavioral history, but not activity level. Additional studies are evaluating the effects of serotonergic antagonists on delta-amphetamine self-injection and noradrenergic antagonists and uptake inhibitors on cocaine self-injection. In another study, we are evaluating the reinforcing efficacy of the stereoisomers of l-deprenyl (selegiline) in comparison to methamphetamine and its l-stereoisomer, as well as evaluating the ability of deprenyl pretreatment to alter self-administration of cocaine, methamphetamine or beta-phenylethylamine

Goldberg SR, Yasar S. Behavioral pharmacology of selegiline (l-deprenyl) and its metabolites and interactions with ß-phenylethylamine, Progress in Brain Research; in press.

Goldberg SR, Youdim MBH. Clinical and preclinical experience with l-deprenyl (selegiline) with regard to abuse liability, Clinical Pharmacology and Therapeutics 1994; in press.

Winger G, Yasar S, Negus SS, Goldberg SR. Intravenous self-administration studies with l-deprenyl (selegiline) in monkeys, Clinical Pharmacology and Therapeutics 1994; in press.

Yasar SY, Bergman J. Amphetamine-like effect of l-deprenyl in drug discrimination studies, Clinical Pharmacology and Therapeutics 1994; in press.

Sannerud CA, Ator NA, Griffiths RR. Behavioral pharmacology of abecarnil in baboons. In: Stephens DN, ed. Anxiolytic ß-carbolines: from molecular biology to the clinic. Psychopharmacology Series II. Berlin: Springer-Verlag, 1993;113-20.

Mumford GK, Evans, SM, Kaminski BJ, Preston KL, Sannerud CA, Silverman,K, Griffiths RR. Discriminative stimulus and subjective effects of theobromine and caffeine in humans, Psychopharmacology 1994;115:1-8.

Sannerud CA, Kaminski BJ, Griffiths RR. Maintenance of H1 antagonists self-injection in baboons, Experimental and Clinical Psychopharmacology 1994; in press.

Sannerud CA, Kaminski BJ, Griffiths RR. Self-injection of phenethylamine" designer drugs" in baboons, Behavioral Pharmacology 1994; in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00002-09 CDM

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Validity Studies of Commercial Drug Screening Assays

PRINCIPAL INVESTIGATOR

P.I.	E.J. Cone, Ph.D.	Chief	Clinical Pharmacology Branch
	W.D. Darwin	Chemist	Clinical Pharmacology Branch
	A. Jenkins	IRTA	Clinical Pharmacology Branch
	D. Yousefnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Commercial assays for the detection of drugs of abuse in urine change periodically and must be reevaluated for performance. Studies are designed to test the validity of new assays with clinical specimens obtained from drug users under controlled conditions.

Healthy male volunteers with a history of chemical substance abuse participate in these studies. Informed consent is obtained and all procedures are approved by the hospital Institutional Review Board. Commercial assays for detection of drugs of abuse in urine are tested for validity with specimens collected under controlled dosing conditions. A variety of drugs of abuse were studied at various dose levels. The results of the assays were compared to GC/MS analysis.

These studies test the validity of commercial assays on clinical samples instead of "spiked" samples and provide unique and valuable information to the military and industry concerning their time course of detection, specificity and accuracy.

Cone, E.J., Dickerson, S.L., Paul, B.D. and Mitchell, J.M., Forensic Drug Testing For Opiates V. Urine Testing For Heroin, Morphine And Codeine With Commercial Opiate Immunoassays. J. Anal. Toxicol., 17: 156-164, 1993.

Jenkins, A.J., Mills, L.C., Darwin, W.D., Huestis, M. A. and Cone, E. J. Validity Testing Of The EZ-Screen: Cannabinoid Test. J. Anal. Toxicol., 17: 292-298, 1993.

Joseph, T., Dickerson, S.L., Willis, R., Frankenfield, D., Cone, E.J. and Smith, D.R. Interference by Nonsteroidal Anti-inflammatory Drugs in EMIT and TDx Assays for Drugs of Abuse. J. Anal. Toxicol., In Press, 1994.

Jenkins, A.J., Darwin, W.D., Huestis, M.A., Cone, E.J. and Mitchell, J.M. Validity Testing of the accu/PINCH THC Test. J. Anal. Toxicol., In Press, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00003-09 BPGS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals

PRINCIPAL INVESTIGATOR

P.I.	Steven Goldberg, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Charles Schindler, Ph.D.	Research Psychologist	Preclinical Pharmacology Laboratory
	Christine Sannerud, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	Sevil Yasar, M.D.	Guest Scientist	Preclinical Pharmacology Laboratory
	Eric Thomdike	Research Psychologist	Preclinical Pharmacology Laboratory
	Mohammed Shoaib, Ph.D.	Visiting Fellow	Preclinical Pharmacology Laboratory

COOPERATING UNITS

Johns Hopkins School of Medicine

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.3	2	1.3

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The behavioral pharmacological profile of a drug in a pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher as well as to establish its stimulus effects. Schedules of food presentation with both fixed-interval and fixed-ratio components have been used most frequently in this type of study since they generate a wide range of rates and patterns of responding within a session and provide stable, long-term baselines for chronic studies in individual animals. The present project involves the assessment of both the acute and chronic effects of a variety of drugs on schedule-controlled behavior. We have recently shown that the enhanced sensitivity observed to the behavioral effects of the opioid antagonist naltrexone is influenced by GABAergic processes, and in particular by an action at the GABA associated chloride channel. Further, this sensitivity may be associated with changes in both mu and delta opioid receptors. Genetic factors are known to influence the behavioral effects of a number of different drugs, and studies of the interactions between environmental and genetic components that potentially affect the development of behavioral tolerance and sensitivity are being initiated. Behaviorally active drugs can also serve as discriminative stimuli to guide behavioral choice. Two- and three-lever drug discrimination projects in the laboratory have helped to define and characterize the spectrum of behavioral effects produced by the drug, to compare a range of other compounds, such as cocaine, l-deprenyl, morphine, midazolam, and caffeine to characterize the relative potency and efficacy to produce drug-like effects, and to evaluate the drug's mechanisms of action at the receptor level. Since most human drug-taking behavior involves chronic long-term use of an illicit drug or non-medical abuse of a prescribed medication, the consequences of chronic administration of drugs on schedule-controlled behavior and the discriminative functions of drugs are being evaluated. Although the development of tolerance and dependence are related to pharmacological factors, tolerance can also be modified by environmental factors. For example, the interaction between drug administration and the ability to perform the task can result in differential tolerance that is a function of chronic daily dose and duration of treatment.

PUBLICATIONS

Sannerud CA, Marley RJ, Serdikoff SL, Alastra AJG, Cohen C, Goldberg, SR. Tolerance to the behavioral effects of chlordiazepoxide: pharmacological and biochemical selectivity, Journal of Pharmacology and Experimental Therapeutics 1993;267:1311-20.

Gauvin DV, Sannerud CA, Young AM. Lack of acute tolerance to the discriminative stimulus effects of morphine in pigeons, Life Sciences 1994; in press.

Sannerud CA, Ator NA. Drug discrimination analysis of midazolam under a three-lever procedure I: dose-dependent differences in generalization and antagonism, Journal of Pharmacology and Experimental Therapeutics 1994; in press.

Persico AM, Schindler CW, O'Hara BF, Brannock MT, Uhl GR. Brain transcription factor expression: effects of acute and chronic amphetamine and injection stress, Molecular Brain Research 1993;20:91-100.

Schindler CW, Persico AM, Uhl GR, Goldberg SR. Behavioral assessment of high-dose amphetamine withdrawal: importance of training and testing conditions, Pharmacology, Biochemistry and Behavior 1994; in press.

Yasar SY, Schindler CW, Thomdike EB, Goldberg SR. Evaluation of deprenyl for cocaine-like discriminative stimulus effects in rats, European Journal of Pharmacology 1994;259:243-250.

Gewiss MV, Marley RJ, Thomdike EB, Goldberg SR, Schindler CW. GABA-receptor linked chloride channels and the behavioral effects of naltrexone in rats, Pharmacology, Biochemistry and Behavior 1994; in press.

Persico AM, Schindler CW, Zaczek R, Brannock MT, Uhl GR. Brain transcription factor gene expression, neurotransmitter levels and novelty response behaviors: alterations during rat amphetamine withdrawal and following chronic injection stress, Synapse 1994; in press.

O-Hara BF, Donovan DM, Lindberg I, Brannock MT, Ricker DD, Moffatt CA, Klaunberg BA, Schindler CW, Chang TS, Nelson RJ, Uhl GR. Proenkephalin transgenic mice: a short promotor confers high testis expression and reduced fertility, Molecular Reproduction and Development 1994;38:275-84.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00009-09 BPGS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Cardiovascular Changes Induced by Cocaine

PRINCIPAL INVESTIGATOR

P.I.	Charles Schindler, Ph.D.	Research Psychologist	Preclinical Pharmacology Laboratory
	Steven Goldberg, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Charles Schuster, Ph.D.	Senior Scientist	Office of the Director
	Srihari Tella, Ph.D.	Guest Scientist	Preclinical Pharmacology Laboratory
	Hashim Ersouki, M.D., Ph.	Visiting Fellow	Preclinical Pharmacology Laboratory
	Eric Thorndike	Research Psychologist	Preclinical Pharmacology Laboratory

COOPERATING UNITS

Georgetown University School of Medicine

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.8	2.6	1.3

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Cardiovascular effects of cocaine are being extensively studied using various species of animals as model systems. Recent investigations have focused on the cocaine metabolites and pyrolysis products, as well as drug interactions. With repeated use of cocaine, the effects of the metabolites may play a more prominent role in the overall effect of cocaine. With the widespread use of "crack" cocaine, the possibility that the pyrolysis products may contribute to cocaine's cardiovascular effects must also be considered. In studies with anesthetized rabbit preparations, injections of small doses of cocaine in the hindbrain of the rabbit produced clear decreases in heart rate, blood pressure and respiratory rate. The same doses give i.v. were without effect, indicating that these depressant effects of cocaine were mediated in the hindbrain. The cocaine metabolite cocaethylene had similar effects, although its effect on respiration was of longer duration. Norcocaine decreased blood pressure but did not affect respiration. The cocaine pyrolysis products also decreased blood pressure and heart rate but increased respiration. The effects of these compounds were comparable when delivered either into the hindbrain or when given i.v., indicating that their effects were not mediated in the hindbrain. These results suggest that the cocaine pyrolysis products do not share a common mechanism of action with cocaine. Cocaine is often used in combination with other drugs. One frequent drug-use combination is that of heroin and cocaine. When given to anesthetized rabbits as a slow, continuous i.v. infusion, cocaine decreased heart rate and blood pressure and increased respiratory rate at higher doses. Heroin also produced decreases in blood pressure and heart rate while decreasing respiration. When given in combination, the hemodynamic effects were exacerbated while cocaine failed to antagonize the respiratory depressant effect of heroin. These results suggest that this drug combination may lead to greater adverse effects than would be predicted from the effects of these drug alone.

Erzouki HK, Allen AC, Newman AH, Goldberg SR, Schindler CW. Effects of cocaine, cocaine metabolites and cocaine pyrolysis products on the hindbrain cardiorespiratory centers of the rabbit, Journal of Cardiovascular Pharmacology 1994; in press.

Erzouki HK, Baum I, Goldberg SR, Schindler CW. Comparison of the effects of cocaine and its metabolites on cardiovascular function in anesthetized rats, J Cardiovas Pharmacol 1993;22:557-63.

Tella SR, Schindler CW, Goldberg SR. Cocaine: Cardiovascular effects in relation to the inhibition of peripheral neuronal monoamine uptake and central stimulation of the sympathoadrenal system, J Pharmacol Exp Ther 1993;267:153-62.

Schindler CW, Wilkerson RD, Gillis RA, Foltin RW, Fischman MW, Newlin D, Levin HR, Goldberg SR. Cardiovascular effects of cocaine: underlying mechanisms. In: Harris L. ed. Problems of drug dependence, 1993, Volume I. National Institute on Drug Abuse Research Monograph 140, 1994; NIH Publication no. 94-3748;79-83.

Schindler CW, Tella SR, Prada J, Goldberg SR. Calcium channel blockers antagonize some of cocaine's cardiovascular effects, but fail to alter cocaine's behavioral effects, J Pharmacol Exp Ther 1994; in press.

Schindler CW, Tella SR, Erzouki HK, Goldberg SR. Pharmacological mechanisms in cocaine's cardiovascular effects, Drug and Alcohol Dependence 1994; in press.

Shah JH, Witkin JM, Tella SR, Nowak G, George C, Newman AH. Quaternary benzazepine analogs lack affinity for dopamine-D1 receptors, Med Chem Res 1994; 3:574-88.

Schindler, CW, Goldberg SR. Conditioned withdrawal. In: Jaffe JH, Clayton RR, Johanson C-E, Kuhar MJ, Moore MH, Sellers EM, eds. The encyclopedia of drugs and alcohol, 1994; in press.

Tella SR, Goldberg SR. Monoamine uptake inhibitors alter pharmacokinetics of cocaine, Psychopharmacology 1993;112:497-502.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00023-09 CDM

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Detection of Drugs of Abuse in Human Saliva

PRINCIPAL INVESTIGATOR

P.I.	E.J. Cone	Chief	Clinical Pharmacology Branch
	W.D. Darwin	Chemist	Clinical Pharmacology Branch
	D. Yousefnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.3	0.1	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The presence of drugs of abuse in saliva of human subjects after drug administration was studied to determine the feasibility of drug testing with saliva as the biological specimen. Healthy subjects with a history of chemical substance abuse volunteered for these studies. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Following the administration of cocaine, marijuana or opiates, saliva and blood samples were collected periodically. Behavioral and physiological measures were made concurrently with collection of biological fluids. Samples were analyzed by radioimmunoassay and gas chromatography/mass spectrometry. Significant correlation's of blood levels with saliva levels were found for cocaine and opiates.

These studies provide the scientific basis for development of new non-invasive saliva tests for drugs of abuse.

PUBLICATIONS

Kato, K., Hillsgrove, M.J., Weinhold, L., Gorelick, D. A., Darwin, W.D. and Cone, E.J.. Cocaine and Metabolite Excretion in Saliva Under Stimulated and Non-Stimulated Conditions. J. Anal. Toxicol., 17: 338-341, 1993.

Cone, E.J. Scientists Study Saliva Testing for Drugs of Abuse. Employment Testing; 2 No. 11, Nov., 93.

Cone, E.J. Saliva Testing for Drugs of Abuse. Ann. NY Acad. Sci. 694: 91-127, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00050-02 CNG

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Assessment of the Causes and Consequences of Drug Dependence

PRINCIPAL INVESTIGATOR

P.I. Roy Pickens, Ph.D. Senior Scientist Office of the Director

COOPERATING UNITS

Michele LaBuda, Johns Hopkins University

LAB/BRANCH

Office of the Director

SECTION

Clinical Neurogenetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☒ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

The primary purpose of this research is to assess the consequences of drug dependence. Drug dependence is thought to have deleterious effects on the individual, producing severe social, behavioral, and medical consequences; however, efforts to quantify these effects have been hampered by a lack of information about the individual prior to drug use. As a result, it is often impossible to determine if an observed clinical condition is the result of drug dependence or is reflective of a preexisting condition. Discordant identical, or monozygotic, twins offer a unique means for assessing the adverse consequences of drug dependence. Because members of monozygotic twins are genetically identical, the study of twin pairs in which only one twin is drug dependent provides a powerful assessment of the effects of drug abuse while controlling for genetic variability. A secondary purpose of the study is the assessment of early experiential differences (both drug-related and non-drug related) to aid in the identification of non-shared environmental factors important in the development of drug dependence.

Through a larger twin study of the genetic influences on drug dependence conducted collaboratively by ARC investigators and Johns Hopkins University, are identifying twin pairs discordant for drug dependence willing to participate in the ARC Discordant Twin Study. The drug-abusing member of each twin pair is housed at the ARC residential unit for a 3-week drug-free period prior to study in order to distinguish between acute effects and long-term consequences of drug use. After this period, a variety of factors associated with drug dependence are assessed including: medical disorders and various metabolic and cardiovascular effects, personality and psychiatric status, neuropsychological performance, and early environmental experiences. Within-pair comparisons in each of these domains will significantly increase our knowledge concerning etiological factors important in drug dependence as well as the effects of long-term drug abuse.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00051-02 CNG

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Comorbidity Between Alcohol, Drug and Mental Disorders

PRINCIPAL INVESTIGATOR

P.I. Roy Pickens, Ph.D. Senior Scientist Office of the Director

COOPERATING UNITS

Michele LaBuda, Ph.D., Johns Hopkins University

LAB/BRANCH

Office of the Director

SECTION

Clinical Neurogenetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

There is significant comorbidity between alcohol, drug and mental disorders in treatment samples and the general population. The basis of this phenomenon is not clear. The co-occurence of these disorders could be due to a common underlying genetic vulnerability or it could be the result of one disorder serving as an environmental influence that predisposes an individual to the other disorders. The elucidation of the etiology of the comorbidity would be important for prevention.

Twin cross-concordant data provide a method for assessing the cause of observed comorbidity. Twins are cross-concordant if one twin is affected with one disorder and the other twin is affected with a second disorder. If there are genetic factors common to both disorders, identical twins would be cross-concordant more often than would fraternal twins. If a significant difference is not found between identical and fraternal twins, the observed relationship between disorders is likely due to environmental factors.

Interpreting cross-concordance data is made difficult by two factors. First, cross-concordance may reflect the independent concordance for the second disorder that may exist within the twin pair. Secondly, cross-concordance may be the result of an environmental association between the two disorders in the cotwin.

Data on comorbid drug and mental disorders in twins with alcoholism will be combined with appropriate control data in order to explore methods of analyzing the etiology of the association between these disorders. Data are available on 169 same-sex twin pairs and analyses will range from simple cross-concordance comparisons to full bivariate cross-twin, cross-trait analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00054-04 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Mother-infant Interactions and CNS Development in Cocaine Exposed Infants

PRINCIPAL INVESTIGATOR

P.I.	C.E. Johanson, Ph.D.	Chief	Etiology Branch
	P.W. Suess, Ph.D.	IRTA	Etiology Branch
	R. Herning, PH.D.	Research Psychologist	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.9	0.9	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Fetal cocaine exposure has been reported to have effects on newborn neurobehavior, sleep and state regulation, and EEG patterns. Early mother-infant interactions have also been shown to be disrupted among drug exposed dyads. The purpose of this study was to investigate CNS development in infants exposed to cocaine in utero and the contribution of variation in maternal interactions to this development. Both cardiac and EEG indices of CNS development were assessed at conceptional ages of 40, 48, and 56 weeks. Mother-infant interactions were observed at 48 and 56 weeks. Mothers and their infants were recruited from area full-term newborn nurseries based on toxicology and self reports of cocaine use during pregnancy. Newborns were tested for cardiac reactivity to an auditory stimulus while still in the nursery. Infant cardiac and sleep EEG were then assessed at the specified ages. Mother-infant interactions were videotaped during a face-to-face play interaction and a feeding. Infant reactivity and temperament as well as maternal psychopathology were assessed.

Analyses of the newborn data revealed that the cocaine-exposed responded with slower habituation of behavioral responses and greater heart rate increase to the first auditory stimulus presentation than the non-exposed. The cocaine-exposed cried more often, experienced more state changes, had shorter intervals of continuous sleep, and exhibited evidence of autonomic instability. These findings support previous studies suggesting poorer habituation among cocaine-exposed neonates and provide new evidence of altered autonomic reactivity to environmental stimuli during the newborn period. Analyses of the EEG recordings collected at follow-up visits revealed well developed sleep state organization in both groups. Sleep state heart rate and vagal tone did not differ between groups. Mothers of cocaine exposed infants tended ($p = .09$) to rate their 56 week infants as more irritable and easily frustrated. During 48 week face-to-face interactions cocaine-exposed infants vocalized more than non-exposed. Mothers of cocaine-exposed used more infantized behaviors and responded more contingently to their infants than control mothers at 56 weeks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00062-02 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Epidemiologic Research Methods

PRINCIPAL INVESTIGATOR

P.I.	H. Chilcoat, Ph.D.	Staff Fellow	Etiology Branch
	C. Johanson, Ph.D.	Chief	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

A primary concern in epidemiologic studies of drug abuse is the development of measurement strategies that are reliable and valid. Not only is it important to develop effective measures of drug abuse outcomes, but also reliable, unbiased measures of related risk factors. Methodologic studies designed to address these concerns will increase confidence in estimates of prevalence and incidence of drug abuse as well as producing indicators of association that are unlikely to be biased. Little is currently known about the reliability of instruments that measure problems related to the use of illicit drugs, including dependence. In particular, there is a relative dearth of information pertaining to test-retest reliability. For this reason, we completed a test-retest study designed to assess the reliability of the substance abuse supplement to the 1991 National Health Interview Survey. This questionnaire consisted of 122 items that assess the use of various drugs in the lifetime and last year, then specifically addresses problems related to the use of marijuana and cocaine which allow generation of dependence diagnosis according to DSM-IIIR criteria. Two hundred seven individuals who entered the recruitment process at the ARC completed the questionnaire at baseline and two weeks later. A random sample of participants (n=97) completed an additional questionnaire two hours after responding to the first questionnaire.

Two-week and two-hour test-retest reliabilities for marijuana and cocaine dependence diagnoses among drug users were generally high. The reliability coefficients (Kappa) for two-week retest of lifetime diagnosis for DSM-IIIR marijuana and cocaine dependence were 0.71 and 0.77, respectively. Two-week reliabilities for dependence diagnoses in the past year were 0.61 for marijuana and 0.79 for cocaine. Reliability coefficients were slightly higher for the two-hour test-retest: lifetime marijuana dependence diagnosis, Kappa = 0.83; lifetime cocaine dependence diagnosis, Kappa = 0.91; past year marijuana dependence diagnosis, Kappa = 0.82; and past year cocaine dependence diagnosis, Kappa = 0.91.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00065-04 BDS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Development of a New Psychometric Instrument for Assessing Drug Cravings

PRINCIPAL INVESTIGATOR

P.I.	Edward Singleton	Senior Staff Fellow	Clinical Pharmacology Branch
	Jack Henningfield	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.5	1.5	2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Among the most ubiquitous effects of addictive drugs, but the least well studied, is drug craving. There has not even existed a validated psychometric instrument for the evaluation of craving that would lend itself to the systematic development of medications for treating drug craving. The Addiction Research Center is presently developing such instrumentation for cocaine, heroin, alcohol, and other drugs of abuse. This research should help us to identify mechanisms of addictive action which are common across drug classes and therefore lead to a better understanding of the mechanisms which underlie the drug cravings. Our initial findings indicated that cocaine craving is a multidimensional construct, involving an admixture of urges and desire, intent to use, loss of control over use, and anticipation of positive outcome. A similar multidimensional structure was found among responses from subjects evaluated using the heroin instrument. One hundred sixty subjects have completed the new Alcohol Craving Questionnaire. The project was modified in June 1993 to include measurement of craving and psychomotor/cognitive testing for outpatient research volunteers and those on the residential unit as a secondary study to examine the relationship between drug cravings and human performance. The Marijuana Craving Questionnaire is under development for administration in FY 1995. The utility of computer administration of the series will be assessed to improve the efficiency of testing. Finally, to extend the generality of the research and investigate ethnic and cultural factors, a Standard Spanish version of the Cocaine Craving Questionnaires and Manual has also been developed.

These advances in instrument development and the enhanced understanding of craving should enable more rapid progress in the ability to produce more selective and efficacious medications and other interventions to meet the needs of those addicted to drugs. With these instruments we should be able to predict which craving dimensions may be relieved by medications and which will require other intervention to enable the person to achieve and sustain drug abstinence.

Tiffany, S.T., Singleton, E.G., Haertzen, C.A. and Henningfield, J.A. The development of a cocaine craving questionnaire. Drug and Alcohol Dependence, 34: 19-28, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00066-06 CDM

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Fast Action Dynamics of Marijuana

PRINCIPAL INVESTIGATOR

P.I.	E.J. Cone	Chief	Clinical Pharmacology Branch
	W.D. Darwin	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Although early changes which occur during the smoking of marijuana are more likely to be indicative of its mode of action, the smoking phase of marijuana use has largely been ignored and very little is known regarding what happens to a human subject during the early phase of smoking.

This study detailed the effects of smoking marijuana cigarettes on a variety of addition, blood and saliva levels were determined during and after smoking. Blood and saliva levels were compared to drug-induced effects and hormonal changes.

The results from this study provide a comprehensive assessment of marijuana's effects that occur both during and after smoking and offer important insight to the mode of action of this widely abused drug.

Cone, E.J. and Huestis, M.A., Do Consecutive Urine Catches Differ In Marijuana Metabolite Concentration? J. Anal. Toxicol., 17: 186-187, 1993.

Huestis, M.A., Mitchell, J.M. and Cone, E.J. Lowering the Federally Mandated Cannabinoid Immunoassay Cutoff Concentration Increases Sensitivity and Efficiency, with Minor Effects on Specificity. Clin. Chem., 40: 729-733, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00076-03 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Dopamine Transporter I: Structure/Function Relationships

PRINCIPAL INVESTIGATOR

P.I.	Stephen Davis, Ph.D.	IRTA	Molecular Neurobiology Branch
	Jia Bei Wang, M.D., Ph.D.	Guest Scientist	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

S. Kityama, DDS., Ph.D, T. Dohi, Hiroshima, Japan
C. Dunigan, A. Shamoo, UMBC
Ivy Carroll, Ph.D., Research Triangle Institute

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The dopamine transporter has been identified as the principal brain receptor site best correlated with the rewarding and euphoric properties of cocaine. We have continued studies using site-directed mutagenesis and molecular modelling and have pursued work with pharmacologic structure/activity studies. These joint strategies aim to identify specific amino acids within the dopamine transporter that are more important for cocaine analog binding than for dopamine uptake, and to identify compounds that could interact with these regions to provide dopamine-sparing cocaine antagonists. In this year we have further defined the nature of the interaction of cocaine with the dopamine transporter. We have used these data to define small molecule lead compounds that might interact with these transporter regions to provide dopamine-sparing cocaine antagonism. More complete understanding of the interactions of dopamine and cocaine with the dopamine transporter should lead to the elucidation of better pharmacological agents useful in the treatment of cocaine abuse.

PUBLICATIONS

Kitayama S, Wang J-B, Uhl GR. Dopamine transporter mutants selectively enhance MPP+ Transport. Synapse 1993;15:58-62

Surratt CK, Wang J-B, Yuhasz S, Amzel M, Kwon HM, Handler JS, Uhl GR. Sodium- and chloride-dependent transporters in brain, kidney, and gut: lessons from cDNA cloning and structure-function studies. In: Hebert SC, Gullans SR, eds. Current opinion in nephrology and hypertension. Pennsylvania: Current Science, 1993;744-60.

Fujita M, Shimada S, Nishimura T, Uhl G, Tohyama M. Ontogeny of dopamine transporter mRNA expression in the rat brain, Mol Brain Res 1993;19:222-6.

Gonzalez AM, Uhl GR. Choline/orphan V8-2-1/creatine transporter mRNA is expressed in nervous, renal and gastrointestinal systems, Mol Brain Res 1994;23:266-70.

Rothman RB, Cadet JL, Akunne HC, Silverthorn ML, Carroll FI, Rice KC, de Costa BR, Partilla JS, Wang JB, Uhl G, Glowa JR, Dersch CM. Studies of the biogenic amine transporters. IV. Demonstration of a multiplicity of binding sites in rat caudate membranes for the cocaine analog [1251]RT1-55, JPET 1994;270(1):296-309.

Kitayama S, Dohi T, Uhl GR. Phorbol esters alter functions of the expressed dopamine transporter, Eur J Pharmacol 1994;268:115-9.

Uhl GR, Johnson PS. Neurotransmitter transporters: three important gene familes for neuronal function, J Exp Biol 1994;in press.

Schindler CW, Persico AM, Uhl GR, Goldberg SR. Behavioral assessment of high-dose amphetamine withdrawal: importance of training and testing conditions, Pharmacol Biochem Behav 1994;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00077-03 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Dopamine Transporter III: Expression and Regulation of mRNA and Protein

PRINCIPAL INVESTIGATOR

P.I.	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch
	Curt Freed, M.D.	IPA	Molecular Neurobiology Branch
	Donna Walther, M.S.	Biologist	Molecular Neurobiology Branch
	Roxanne Vaughan, Ph.D.	Staff Fellow	Neuroscience Branch
	Michael Kuhar, Ph.D.	Chief	Neuroscience Branch
	Catherine Cerrutti, Ph.D.	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The dopamine transporter is a principal site for cocaine's rewarding and euphoric effects in the brain. Cocaine analog binding studies have revealed some details of the regional distribution of this transporter in untreated and in cocaine-treated brains. Studies completed during this FY have substantially enhanced information concerning the distribution of dopamine transporter protein, using immunohistochemical approaches. They also elucidated cell-group-specific alterations in transporter gene expression in animals withdrawn from a regimen of chronic cocaine administration.

Blanchard V, Raisman-Vozari R, Vyas S, Michel PP, Javoy-Agid F, Uhl G, Agid Y. Differential expression of tyrosine hydroxylase and membrane dopamine transporter genes in subpopulations of dopaminergic neurons of the rat mesencephalon, Mol Brain Res 1994;22(1-4):29-38.

Cerruti C, Pilotte NS, Uhl G, Kuhar MJ. Reduction in dopamine transporter mRNA after cessation of repeated cocaine administration, Mol Brain Res 1994;22:132-8.

Gonzalez AM, Walther D, Pazos A, Uhl GR. Synaptic vesicular monoamine transporter expression: distribution and pharmacologic profile, Mol Brain Res 1994;22:219-26.

Uhl GR, Walther D, Mash D, Faucheux B, Javoy-Agid F. Dopamine transporter Messenger RNA in Parkinson's disease and control substantia nigra neurons, Ann Neurol 1994;35:494-8.

Freed CR, Revay R, Vaughan RA, Kriek E, Grant S, Uhl GR, Kuhar MJ. Dopamine transporter immunoreactivity in rat brain, J Comp Neurol 1994;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00079-03 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Dopamine Transporter II: Human and Mouse Genes and Dopaminergic Disorders

PRINCIPAL INVESTIGATOR

P.I.	David Vandenbergh, Ph.D.	Senior Staff Fellow	Molecular Neurobiology Branch
	David Donovan, Ph.D.	Senior Staff Fellow	Molecular Neurobiology Branch
	Lawrence Sharp, Ph.D.	Pharmacologist	Molecular Neurobiology Branch
	Jean-Claude Martel, Ph.D.	Visiting Fellow	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

J. Gelemter, Yale University
E. Gershon, NIMH
O. Hurko, Johns Hopkins

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.1	1.35	0.75

CHECK APPROPRIATE BOXES

☐ (A) Human ☒ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The dopamine transporter/cocaine receptor (DAT) is the site at which cocaine experts rewarding/reinforcing effects and plays a central role in termination of dopamine neurotransmission. This gene is expressed most prominently in just those dopaminergic neurons most implicated in cocaine's psychomotor stimulant effects. We have isolated genomic clones of the human and mouse DAT genes that contain the 5' flanking sequences, and have begun work to identify the promoter for this gene, in order to provide means for selective overexpression of genes in just these dopaminergic neuronal populations. This work also allows identification and study of new gene polymorhpisms that can serve as gene markers to enhance power of genetic analysis of DAT roles in neuropsychiatric disorders. Knowledge of the promoter and gene structure will allow transgenic mice that have modified dopamine transporters or modified expression of the genetic repertoire of dopaminergic neurons to be studied as potential animal models for human substance abuse disorders.

Nearly complete human gene and partial mouse gene sequences have been identified and characterized. A short human DAT promoter sequence appears to drive expression of a reporter gene in dopaminergic neurons as well as non-dopaminergic neurons of the brain.

Persico AM, Vandenbergh DJ, Smith SS, Uhl GR. Dopamine transporter gene polymorphisms are not associated with polysubstance abuse. Biol Psychiatry 1993;34:265-7.

O'Hara BF, Donovan DM, Lindberg I, Brannock MT, Ricker DD, Moffatt CA, Klaunberg BA, Schindler C, Chang TSK, Nelson RJ, Uhl GR. Proenkephalin transgenic mice: a short promoter confers high testis expression and reduced fertility, Mol Reprod Dev 1994;38:275-84.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00084-03 GS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Biochemical and Behavioral Consequences of Brain-Region-Specific Expression

PRINCIPAL INVESTIGATOR

P.I.	David Donovan, Ph.D.	Sr. Staff Fellow	Molecular Neurobiology Branch
	Lucinda Miner, Ph.D.	Sr. Staff Fellow	Molecular Neurobiology Branch
	Ichiro Sora, M.D., Ph.D.	Visiting Fellow	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch
	Dona Walther, M.D.	Biologist	Molecular Neurobiology Branch
	Michael Perry, M.S.	Biologist	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Genetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.25	0.75	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

There are large individual differences among humans and animals in behavioral, physiological and toxicological responses to drugs of abuse. Many of these individual differences in behavioral responses to drugs display substantial genetic components. Transgenic animals provide means for approaching three interrelated goals: 1) Identification of gene elements that confer cell-type specific expression and may thus allow targeting of introduced genetic material to appropriate brain regions; 2) Elucidation of gene elements yielding trans-synaptic gene regulation and thus allowing appropriate regulated expression of introduced genetic material; and 3) Ascertainment of biochemical and behavioral consequences of the introduction of or disruption of specific genes.

Dopaminergic systems' involvement in central mechanisms of reward and reinforcement, and involvement of pre- and post-synaptic opioid peptide systems in the effects of opiate drugs has led to focus on these systems during this FY. Elements in the dopamine transporter gene's 5' flanking region that might confer its exquisite dopamine cell-specific expression were sought by cloning more than 24 kb of this sequence, and examining expression in different cultured cells and in transgenic animals. Tyrosine hydroxylase promoter, which can provide catecholamine-specific gene expression, was used to drive expression of dopamine transporter, interesting transporter mutants, and mu opiate receptor cDNAs. Preliminary analyses appear to reveal brain expression of mRNA but less expression of protein, while initial behavioral studies indicate a variable influence of transporter overexpression on exploratory, habituation, and cocaine-responsive behaviors.

PUBLICATIONS

Uhl GR, Takemura M. Gene mechanisms in primary afferent proenkephalin regulation in nucleus caudalis. In:Inoki R, Shigenaga Y, Tohyama M, eds. Processing and inhibition of nociceptive information. The Netherlands: Elsevier Science Publishers B.V., 1992;103-8.

Uhl GR. A review of in situ hybridization techniques: relevance to combined immunocytochemical studies. In: Cuello AC, ed. Immunohistochemistry. England: John Wiley & Sons, 1993;Second Edition, Chapter 9, 281-300.

Marota JAJ, Crosby G, Uhl GR. Selective effects of pentobarbital and halothane on c-fos and jun-B gene expression in rat brain, Anesthesiology 1992;77:365-71.

Walther D, Takemura M, Uhl G. FOS family member changes in nucleus caudalis neurons after primary afferent stimulation: enhancement of fos B and c-fos, Mol Brain Res 1993;17:155-9.

Uhl GR. Identifying and localizing gene expression important for the actions of abused drugs. In: London L, ed. Imaging drug action in the brain. Boca Raton: CRC Press, 1993;14:379-404.

O'Hara BF, Donovan DM, Lindberg I, Brannock MT, Ricker DD, Moffatt CA, Klaunberg BA, Schindler C, Chang TSK, Nelson RJ, Uhl GR. Proenkephalin transgenic mice: a short promoter confers high testis expression and reduced fertility, Mol Reprod Dev 1994;38:275-84.

Crosby G, Marota JJA, Uhl GR. Preproenkephalin gene expression in rat spinal cord following subarachnoid analgesia with morphine or clonidine, Anesthesiology 1993;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00087-03 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Identification of Psychostimulant- and Opiate-Inducible Genes in Brain

PRINCIPAL INVESTIGATOR

P.I. Xiao-Bing Wang, M.D., Ph. Visiting Fellow — Molecular Neurobiology Branch

George Uhl, M.D., Ph.D. Chief — Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Psychostimulants and opiates are know to induce behavioral dependence syndromes that are presumed to be mediated by corresponding long-term changes in the central nervous system. Alterations in protein synthesis and/or gene expression are strong candidate mechanisms to play roles in these processes. Work in this laboratory during previous FYs has documented that psychostimulants and opiates can modify the expression of several DNA-binding transcription factors in specific brain regions. However, which genes are regulated by those transcription factors remain largely unknown. Differential display following polymerase chain reaction amplification (PCR-DD) provides a powerful new tool to identify such genes whose expression levels are altered by drugs. During this FY, we have identified interesting candidate genes for involvement in dependence mechanisms through this approach.

PUBLICATIONS

Persico AM, Schindler CW, O'Hara BF, Brannock MT, Uhl GR. Brain transcription factor expression: effects of acute and chronic amphetamine and injection stress. Mol Brain Res 1993;20:91-100

Persico A, Schindler CW, Zaczek R, Brannock MT, Uhl GR. Brain transcription factor gene expression, neurotransmitter levels and novelty response behaviors: Alterations during rat amphetamine withdrawal and following chronic injection expression, Synapse 1994;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00089-03 BPGS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Analysis of the Neural Substrates Mediating the Motivational Effects of Opiates

PRINCIPAL INVESTIGATOR

P.I.	Toni Shippenberg, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	Steven Goldberg, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Christian Heidbreder, Ph.D	Visiting Fellow	Preclinical Pharmacology Laboratory
	Taco De Vries, M.D., Ph.D	Guest Scientist	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.8	2.8	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The mesocorticolimbic dopamine (DA) system has been implicated in mediating the rewarding effects of various drugs of abuse. An involvement of this system in the development of drug-induced tolerance, withdrawal and sensitization, phenomenon which are thought to play a role in drug-craving and relapse, has more recently been postulated. Evidence that opioidergic neurons can modulate the activity of this system has also been presented. Given the apparent involvement of both DAergic and opioidergic neurons in the addiction process, ongoing studies are seeking to determine: i) whether manipulations which alter their neuronal activity can modify the pharmacological and/or neurochemical effects of psychoactive drugs and ii) whether differences in the basal activity of DAergic and/or opioidergic systems or their responsivity to drugs of abuse underlie individual differences in compulsive drug-seeking behavior. Classical (place preference conditioning) and operant (drug discrimination, self-administration) conditioning techniques are being used to characterize the rewarding effects of opioids and psychostimulants and to identify pharmacological treatments which lead to or prevent the development of drug dependence and sensitization. In-vivo microdialysis combined with HPLC and electrochemical detection is being used to quantitate neurotransmitter release/metabolism within the mesocorticolimbic system in response to various psychoactive drugs. Identical studies using inbred rat strains as well as animals with a history of pre/post natal drug exposure are being conducted to identify those factors, both endogneous and exogenous which may underlie vulnerability to drug abuse.

Heidbreder Ch, Goldberg SR, Shippenberg TS. Inhibition of cocaine-induced sensitization by the delta opioid receptor antagonist naltrindole, Eur J Pharmacol 1993;243:123-71.

Heidbreder Ch, Shippenberg TS. U69593 prevents cocaine sensitization by normalizing basal accumbens dopamine, Neuroreport 1994; in press.

Heidbreder Ch, Shippenberg TS. Sensitization to the conditioned rewarding effects of cocaine, NIDA Research Monograph; in press.

Heidbreder Ch, Shippenberg TS. High basal dopamine tone in the nucleus accumbens blunts the response profile to repeated cocaine exposure. In: Louilot L, Cador M, eds. In-vivo methods for the monitoring of molecules, Bordeaux, Inserme 1994; in press.

Schutz C, Ambrosio E, Shippenberg TS, Elmer G, Heidbreder Ch. Morphine-induced locomotor activity and dopamine overflow in the nucleus accumbens in Lewis and Fischer rats: a comparative study. In: Louilot L, Cador M, eds. In-vivo methods for the monitoring of molecules, Bordeaux, Inserme 1994; in press.

Shippenberg TS, Bals-Kubik R. Involvement of the mesolimbic dopamine system in mediating the aversive effects of opioid antagonists in the rat, Behav Pharmacol 1994; in press.

Shippenberg TS, Heidbreder Ch. Role of kappa- and delta opioid systems in modulating sensitization to the rewarding effects of cocaine, Reg Peptides 1994; in press.

Shippenberg TS, Heidbreder Ch. Sensitization to the conditioned rewarding effects of cocaine: pharmacological and temporal aspects, J Pharmacol Exp Therap 1994; in press.

Shippenberg TS, Heidbreder, Ch. Kappa opioid receptor agonists prevent sensitization to the rewarding effects of cocaine. NIDA Research Monograph, 1994; in press.

Shippenberg TS, Spanagel R, Heidbreder Ch. Modulation of mesolimbic dopamine release by endogenous opioids; role in drug-induced sensitization and dependence. In: Louilot L, Cador M, eds. In-vivo methods for the monitoring of molecules, Bordeaux, Inserme 1994; in press.

Shoaib M, Shippenberg TS. Contrasting effects of adrenalectomy on nicotine-induced dopamine release and locomotor depression in rats. In: Louilot L, Cador M, eds. In-vivo methods for the monitoring of molecules, Bordeaux, Inserme 1994; in press.

Shoaib M, Spanagel R, Stohr T, Shippenberg TS. Strain difference in the rewarding and dopamine releasing effects of morphine in rats, Psychopharmacology 1994; in press.

Spanagel R, Almedia OFX, Shippenberg TS. Long-lasting changes in morphine-induced mesolimbic dopamine release after chronic morphine exposure, Synapse 1993;243-5.

Spanagel R, Almeida OFX , Bartl C, Shippenberg TS. Endogenous kappa opioid systems in opiate withdrawal: role in aversion and accompanying changes in mesolimbic dopamine release, Psychopharmacology 1994;115:121-7.

Spanagel R, Shippenberg TS. Evidence that nor binaltorphimine (nor-BNI) can function as an antagonist at multiple opioid receptor types, Eur J Pharmacol 1994; in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00093-03 BDS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Pupillometric studies of drug actions

PRINCIPAL INVESTIGATOR

P.I.	Wallace Pickworth	Research Pharmacologist	Clinical Pharmacology Branch
	Jack Henningfield	Chief	Clinical Pharmacology Branch
	Edward Cone	Chief	Clinical Pharmacology Branch
	Ivan Montoya	Visiting Fellow	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The effects of drugs on pupil size are among the most easily detected and characteristic signs of drug action. Several animal studies conducted at the ARC have clarified the neural mechanisms through which psychoactive drugs influence pupil diameter and the light reflex. This research has been extended to clinical studies where the pupillary effects of several classes of abused drugs were compared to their performance and subjective effects. Additional research on retinal physiology using newly developed pupillometers has yielded new information of the retinal processing of the light reflex. Since retinal neural organization mimics brain neural systems, it is proposed that the influence of drugs in this system indicates drug mechanisms elsewhere in the brain. Dependent measures of these studies include pupil size, constriction and dilation velocities of the light reflex, smooth pursuit, and saccadic tracking. These studies are typically within subject repeated measure design, and drugs are administered in a double blind and placebo controlled design Progress to date includes studies of the effects of marijuana, ethanol, cocaine, opiates amphetamine have been studies after various routes of administration.

Fosnaugh, J.S. Bunker, E.B., Pickworth, W.B. Daily variation and effects of ambient light and circadian factors on the human light reflex. Methods and Findings in Clinical and Experimental Pharmacology 14:545-553, 1992.

Rothman, R.B., Gorelick, D.A., Guo, X.Y., Heming, R.I. Pickworth, W.B., Gendron, T.M., Koeppl, B., Thomson. L.E. III, and Henningfield, J.E. Lack of evidence for context-dependent cocaine-induced sensitization. Pharmacology Biochemistry and Behavior 1994 (in press).

Pickworth, W.B., Johnson, R.E. Holicky, B.A., and Cone, E.J. Subjective and physysiologic effects of buprenorphine in humans. Clinical Pharmacology and Therapeutics 53:570-576, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00101-09 BPGS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Pharmacogenetics: Acute Response to Drug Administration

PRINCIPAL INVESTIGATOR

P.I.	Gregory Elmer, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	Steven Goldberg, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Richard Rothman, M.D., P	Chief	Clinical Pharmacology Branch
	Jean Cadet, M.D.	Chief	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.25	0.75	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

A major research emphasis in the last year has been to utilize the behavior genetics method and a classical pharmacological approach to determine genetic and pharmacological contributions to characteristics important in the acute effects of opioids. In particular, delta-opioid subtypes have recently been proposed based upon differential antagonism and no cross tolerance between the delta-agonists, DPDPE and deltorphin II. In order to determine the existance of delta-receptor subtypes and determine the degree of genetic covariance between the proposed subtypes full dose-response curves for DPDPE and deltorphin II were determined in eight inbred mouse strains. The correlation between sensitivity to DPDPE- and deltorphin II-induced analgesia was not significant thus supporting a pharmacological and genetic separation of the two delta-receptor subtypes. Two inbred strains that lacked a delta-2 response and a strain in which the mu agonist morphine acts like a delta-agonist were used in combination with other inbred strains to investigate the interactions of the delta-2 subtype with delta-1 and mu-agonists. Cross-over pretreatment experiments with the two delta-agonists suggest that deltorphin II is not unique in its pharmacology due to partial agonist properties but is pharmacologically and genetically distinct in its mechanism of action. In the interaction experiments, the 2 strains lacking delta-2 agonist effects and the strain in which morphine acts via delta-mechanisms, deltorphin II did not shift the morphine dose-response curve. Initial biochemical studies done in collaboration with the Clinical Psychopharmacology Section verify the absence of a delta-receptor subtype in the CBA strain and may provide a unique 'd knockout' strain for investigating the role of this d-receptor subtype in the acute and chronic effects of abused drugs. The data provied in these experiments are being compared to transgenic mice that display increased mu-receptor Bmax (superoxide dismutase transgene addition, Molecular Neuropsychiatry Section) in order to explore the in vivo consequences of altered mu and delta receptor regulation on the acute and chronic affects of abused drugs

Borisova E, Sudakov S, Elmer GI, Goldberg SR. Action of thyrotropin releasing hormone on morphine-induced analgesia and preference in two inbred rat strains. Pharmacology, Biochemistry and Behavior 1994; in press.

Elmer GI, George FR. Rate depressant effects of ethanol in selectively bred mice: relationship to acute neurosensitivity to ethanol. Journal of Addictive Diseases 1994;13:9-19.

Elmer GI, George FR. Antagonism of ethanol-induced narcosis by RO15-4513 and indomethacin. Alcoholism: Clinical and Experimental Research 1994; in press.

Goodman CG, Elmer GI, Yang H-YT, Lee CH, Rothman RB. Modulation of opioid receptors by antiopioid peptides. In: Tseng LF, ed. Pharmacology of opioid peptides. Harwood Academy Publishing, 1994; in press.

Marley JM, Elmer GI, Goldberg SR. The use of pharmacogenetic techniques in drug abuse research, Pharmacology and Therapeutics 1993;53:217-37.

Marley JM, Shimosato K, Elmer GI, Miner LL. Pharmacogenetic approaches to drug dependence. In: Wonnacott S, Lunt GG, eds. Neurochemistry of drug dependence, Portland Press, London 1993;59:153-72.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00103-05 BPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Basic Mechanisms of Cocaine's Behavioral Effects

PRINCIPAL INVESTIGATOR

P.I.	J. Katz, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	J. Witkin, Ph.D.	Research Psychologist	Preclinical Pharmacology Laboratory
	A Newman, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	S. Izzenwasser, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	R. Klien, Ph.D.	Guest Scientist	Preclinical Pharmacology Laboratory
	A. Allen, Ph.D.	Guest Scientist	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Psychobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4.9	3.9	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The primary focus of this research is to develop a better understanding of the pharmacological mechanisms underlying the behavioral effects of cocaine that lead to its abuse and the consequences of that abuse. Studies have indicated that: (1) The psychomotor stimulant effects of cocaine, as indicated by increases in locomotor activity, are mediated by both D1 and D2 dopamine receptors. For increase in learned operant behavior produced by cocaine, however, D2 receptors have a greater involvement than do D1 receptors. The respective roles of other dopamine receptors are currently under investigation. (2) There are differences among dopamine uptake inhibitors in the relationships of their beavioral effects and their affinity for the dopamine transporter. For drugs that have a structural similarity to cocaine there is a direct relation between affinity for the transporter and in vivo potency. In contrast, for structurally dissimilar compounds their is no simple relationship. These data indicate that cocaine and its congeners bind to the dopamine transporter in a manner that is distinct from that of other dopamine uptake inhibitors. (3) The subjective behavioral effects of cocaine are mediated by both D1 and D2 dopamine receptor systems, although actions through either system alone are not sufficient to fully reporduce the subjective effects of cocaine. (4) The subjective behavioral effects of low doses of cocaine are mediated by both D1 and D2 dopamine receptor systems, although actions through the D1 dopamine system appear to predominate. In addition, the subjective effects of low doses of cocaine have a significant noradrenergic component that is not evident in the effects of higher doses of cocaine. (5) Anhydroecgonine methyl ester (AEME) is a major pyrolysis product of cocaine and has been detected in high concentration in the urine of subjects who have smoked "crack." In addition, AEME has a structural resemblence to anatoxin-A, a known cholinergic toxin. The contribution of AEME to the unique pharmacological actions of "crack" was investigated. These studies found that AEME probably does not contribute in a significant way to the stimulant or subjective effects of "crack" or its toxicity. (6) Tolerance to the behavioral effects of cocaine is not accompanied by changes in the function of dopamine D1 receptors. Further studies are being conducted to assess the effects of cocaine treatment on functional aspects of other dopamine receptor subtypes. (7) Unique compounds have been synthesized that have high affinity for the dopamine transporter and inhibit dopamine uptake. However, these drugs do not have behavioral effects that are similar to those of cocaine. Initial structure-activity studies indicate that the binding of these compounds to the dopamine transporter is different from that for cocaine. Because these compounds bind to the dopamine transporter but do not have cocaine-like behavioral effects, they may serve as cocaine antagonists, which is currently under investigation.

Erzouki HK, Allen AC, Newman AH, Goldberg SR, Schindler CW. Effects of cocaine, Cocaine metabolites and cocaine pyrolysis products on the hindbrain cardiorespiratory centers of the rabbit, Journal of Cardiovascular Pharmacology, In Press, 1994.

Izenwasser S, Terry P, Heller B, Witkin JM, Katz JL. Differential relationships among dopamine transporter affinities and stimulant potencies of various uptake inhibitors, European Journal of Pharmacology, In Press, 1994.

Newman AH, Allen AC, Izenwasser S, Katz JL. Novel 3alpha-diphenylmethoxytropane analogs are potent dopamine uptake inhibitors without cocaine-like behavioral profiles, Journal of Medicinal Chemistry 1994;37:2285-91.

Newman AH, Allen AC, Witkin JM, Izenwasser S, Mash D. Katz JL. The thermal decomposition product of "crack," AEME, and analogs do not appear to contribute acutely to the pharmacological or toxicological actions of cocaine, Medicinal Chemistry Research 1994;4:93-110.

Terry P, Witkin JM, Katz JL. Pharmacological characterization of the novel discriminative stimulus effects of a low dose of cocaine, Journal of Pharmacology and Experimental Therapeutics, In Press, 1994.

Tirelli E, Witkin JM. Transient hypersensitivity to apomorphine-induced gnawing after termination of acute effects of a single high doses of cocaine, Behavioural Pharmacology 1994;5:289-98.

Witkin JM. Pharmacotherapy of cocaine abuse: Preclinical development, Neuroscience and Biobehavioral Reviews 1994;18:121-42.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00104-05 BPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Drug Development

PRINCIPAL INVESTIGATOR

P.I.	J. Witkin	Research Psychologist	Preclinical Pharmacology Laboratory
	J. Katz	Chief	Preclinical Pharmacology Laboratory
	A Newman	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	S. Izenwasser	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	J. Shah	IRTA	Preclinical Pharmacology Laboratory
	J. Arci	IRTA	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Psychobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4.9	3.9	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

These studies are designed to provide preclinical information for the development of medications to be used in the treatment of drug abuse and drug abuse-related toxicities. The primary focus of this work is to determine pharmacological means for modulating behavioral and toxic actions of abused compounds, and to evaluate new chemical entities (synthesized in house and from outside sources) for safety and efficacy in the design of potential rational treatment strategies. Work in this area is also expected to provide increased understanding of the mechanisms of action of drugs of abuse. The primary findings and implications for the current year are: (1) We have extended initial observations that certain sigma-receptor ligands can antagonize some of the acute behavioral effects of cocaine by demonstrating this effect with a highly selective sigma ligand and by showing that this compound can also attenuate the behavioral effects of repeated cocaine exposure (sensitization) and cocaine-induced convulsions. We have also found that certain sigma ligands bind to the dopamine transporter. Ongoing studies are focusing on identifying significant features of sigma ligands that imbue them with the ability to block effects of cocaine and defining a mechanism for the cocaine blockade. A host of sigma ligands, some with excellent affinity and selectivity have been synthesized to aid in this effort. (2) A variety of compounds proposed by NIDA as potential treatments for cocaine abuse are being examined in preclinical screens for safety and efficacy as potential treatments for cocaine abuse. (3) Psychomotor stimulant effects of abused drugs like cocaine may be amenable to pharmacological antagonism through glutamate receptors. We have discovered some such compounds with efficacy as antagonists of the stimulant effects of cocaine and of methamphetamine and have uncovered differences among these compounds which should help shed light on the interactions between dopaminergic and excitatory amino acid pathways. (4) In accord with clinical experience, we have used a model developed in our lab of cocaine-induced convulsions that are relatively insensitive to standard anticonvulsants to discover novel and efficacious treatments for drug-resistant cocaine toxicities. Thus far, a host of glutamate antagonists have been shown to be effective and some appear to have a reasonable margin of safety for this therapeutic endpoint. Two classes of compounds have been identified for further drug development, low affinity NMDA antagonists and functional antagonists of the glycine-linked site of the NMDA receptor. (5) Pharmacological studies have tentatively identified a population of dopamine D1 receptors in the periphery that may be linked to the acute lethal effects of cocaine. Compounds necessary for further investigations in this area have been synthesized and structure-activity relationships, and in vitro and in vivo pharmacological characterization of these compounds is underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00105-05 BPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Pharmacology of Dopamine Systems

PRINCIPAL INVESTIGATOR

P.I.	J. Katz	Chief	Preclinical Pharmacology Laboratory
	J. Witkin	Research Psychologist	Preclinical Pharmacology Laboratory
	S. Izenwasser	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	A Newman	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	P. Terry	Visiting Fellow	Preclinical Pharmacology Laboratory
	J. Shah	IRTA	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Psychobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4.9	3.9	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The dopaminergic system is clearly implicated as important in mediating the effects of many drugs of abuse, as well as Parkinsons disease, and schizophrenia. Our studies have as their goals the determination of the functional significance of the dopamine system in normal functioning, as well as how it acts to subserve drug abuse. One specific objective is to better characterize the pharmacology of the various subtypes of CNS dopamine receptors. Included in this goal is the identification of drugs that act selectively and with high efficacy. In many cases the pharmacological tools for the study of these receptor subtypes in vivo and in vitro are limited. As a result, one further goal is the discovery of new synthetic entities that will allow analysis of the pharmacology of these dopamine receptor subtypes. These studies indicate that: (1) While it is possible to differentiate D1 dopamine agonists in vitro on the basis of their intrinsic efficacy, differences in the efficacy of the drugs have not been correlated with any other observed pharmacological effect of these drugs. (2) Studies of the behavioral effects of the D1 dopamine agonist, SKF 38393, have indicated few of its behavioral effects are mediated by actions at D1 dopamine receptors. This finding is important because SKF 38393 is often used as a prototype D1 agonist. (3) Dopamine D1, but not dopamine D2, receptors are involved in the lethal effects of acutely administered cocaine. We are preparing D1 antagonists that do not penetrate the blood brain barrier. These drugs may serve as antidotes to acute cocaine overdose and will also serve as tools for the investigation of the function of the peripheral D1 dopamine system. (4) Dopamine D2 agonists can stimulate this behavior in a manner similar to the manner in which cocaine or amphetamine stimulate behavior, in contrast, D1 agonists do not. These differences suggest an involvement of D2 dopamine receptors in the stimulant behavioral effects, and a lack of involvement of D1 dopamine receptors. (5) The pharmacology of dopamine D2 agonists is being characterized in a cell line that expresses a D2 receptor that is functionally similar to brain dopamine D2 receptors. Because these D2 receptors are expressed in the absence of other dopamine receptor subtypes, this cell line is a model system for studying the function and regulation of the D2 receptor. The findings from these studies suggest that the dopamine D2 receptor regulates cyclase inhibition predominantly via the Gi1 and/or Gi2 subunits of G-alpha. Using this system the intrinsic efficacies of dopamine D2 agonists have been characterized. These studies also indicated an intriguing link between the Gi3 subunit and the Gi1 or Gi2 subunits. (6) The pharmacology of the putative D3 receptor agonist, 7-OH-DPAT, is being characterized. These behavioral and in vitro studies have indicated that 7-OH-DPAT is a weak partial agonist at D2 receptors, and its several of its effects may be mediated by that activity rather than D3 agonist

Izenwasser S, Katz JL. 7-OH-DPAT antagonizes dopamine D2 receptor-inhibited adenylyl cyclase activity, Life Sciences 1994; 55:PL257-9.

Izenwasser S, Cote TE. Inhibition of adenylyl cyclase by a homogeneous population of dopamine D2 receptors: Selective blockade by antisera directed against Gi1 and/or Gi2, Journal of Neurochemistry, In Press, 1994.

Pellón R, Flores P, Alling K, Witkin JM, Katz JL. Pharmacological analysis of the scratching produced by dopamine D2 agonists in squirrel monkeys, Journal of Pharmacology and Experimental Therapeutics, In Press. 1994.

Terry P, Katz JL. A comparison of the effects of D-1 receptor antagonists SCH 23390 and SCH 39166 on suppression of feeding behavior by the D-1 agonist SKF 38393, Psychopharmacology 1994;113:328-33.

Tirelli E, Witkin JM. Verticalization of behavior elicited by dopaminergic mobilization is qualitatively different between C57BL/6J and DBA/2J mice, Psychopharmacology, In Press, 1994.

Tirelli E, Witkin J M. Differentiation between direct and indirect dopamine agonists via their effects on gnawing in C57B1/6J mice, Journal of Pharmacology and Experimental Therapeutics, In Press, 1994.

Tirelli E, Witkin JM. Transient hypersensitivity to apomorphine-induced gnawing after termination of acute effects of a single high doses of cocaine, Behavioural Pharmacology 1994;5:289-98.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00107-09 MPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Drug Receptors in Vivo: Animal Models and Imaging

PRINCIPAL INVESTIGATOR

P.I.	Michael J. Kuhar, Ph.D.	Chief	Neuroscience Branch
	John Boja, Ph.D.	Sr. Staff Fellow	Neuroscience Branch
	Elizabeth Cline, Ph.D.	Pratt Fellow	Neuroscience Branch
	Elias Shaya, Ph.D.	Staff Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1.5	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Almost all of our knowledge of drug receptors comes from in vitro experiments. However, it is important to study receptors in vivo for many reasons. Accordingly, one of our goals is to develop ligands and approaches for studying drug receptor sites in human populations by imaging techniques. Prior to imaging in humans, ligands need to be developed and tested in vitro and in vivo in animals.

In our structure-activity studies of the cocaine receptor, RTI-55 was identified as a very potent compound with a high affinity for the dopamine transporter. It also has some affinity for the serotonin transporter as well. Accordingly, our previous publications show that RTI-55 is an excellent PET and SPECT ligand for studying dopamine transporters in vivo. It has been patented, licensed and is currently being used in several centers as an imaging reagent for diagnosing Parkinson's disease.

Because of its significant affinity for serotonin transporters, it is possible to use RTI-55 as an in vivo binding ligand to study the occupancy of serotonin transporters by relevant drugs. We have examined the important newer antidepressant drugs which have a selective affinity for the serotonin transporter. Radiolabeled RTI-55 was administered and in vivo competition was carried out with fluoxetine, paroxetine and sertraline. At behaviorally effective doses, it was clear that these drugs occupied the serotonin transporter. Also, fluoxetine which is known to have a longer half-life in human subjects, had a much longer half-life in these animal studies than the other compounds. These results indicate that RTI-55 can be used to study the serotonin transporter, in particular to identify drugs that bind to that site, to determine the relative rate of occupancy, and also determine the duration of action of compounds at this site.

We have previously utilized radiolabeled WIN-35,428 as a PET ligand to bind to dopamine transporters in vivo. In a recent study, we examined the kinetics and pharmacology of this binding in animals and humans. We clearly show that this compound is a promising radioligand for future studies of neuropsychiatric disorders that involve the dopamine transporter site.

Wong D.F, Yung B., Dannals R.F., Shaya E.K., Ravert H.T., Chen C.A., Chan B., Folio T., Scheffel U., Ricaurte G.A., Neumeyer J.L., Wagner H.N., Jr. and Kuhar M.J. In Vivo Imaging of Baboon and Human Dopamine Transporters by Positron Emission Tomography Using [11C]WIN 35,428. Synapse, 15, 130-142, 1993.

Scheffel U., Kim S., Cline E.J. and Kuhar M.J. Occupancy of the Serotonin Transporter by Fluoxetine, Paroxetine, and Sertraline: In Vivo Studies With [125I]RTI-55. Synapse 16, 263-268, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00108-07 MPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

The Cocaine Receptor: Structure Activity Relationships and Ligand Binding Studies

PRINCIPAL INVESTIGATOR

P.I.	M.J. Kuhar, Ph.D.	Chief	Neuroscience Branch
	J. Boja, Ph.D.	Sr. Staff Fellow	Molecular Neurobiology Brancn
	B. Blough, Ph.D.	IRTA	Neuroscience Branch

COOPERATING UNITS

F.I. Carroll, Research Triangle Institute

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4	2	2

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The goal of this project is to explore the interaction of cocaine and cocaine-like compounds with their binding sites in brain. The binding site or "receptor" thought important for the reinforcing effects of cocaine, at least in animals, is the dopamine transporter. Other effects of cocaine and its congeners are likely to be due to interaction at other sites such as other transporters. Besides developing an understanding of the interaction of cocaine with transporters, this study also reveals potent reversible and irreversible binding ligands for in vitro and in vivo studies of transporter proteins. Some compounds may be useful as treatment medications as well.

Several classes of cocaine analogs were tested in binding and uptake studies at the dopamine transporter, and sometimes also at the norepinephrine and serotonin transporters. These studies were carried out using rat brain tissue although sometime human brain tissue was utilized as well. The methods employed were standard radiolabeled ligand binding techniques.

Cocaine has a carbomethoxy group in the C-2 position which is required for its activity. Since oxadiazoles are excellent bioisosteres of ester groups, several oxadiazoles were synthesized and tested in binding assays. In general, these compounds showed potencies for the dopamine transporter similar to the parent esters. The most potent analog had an IC-50 of 1.6 nM, and selectiveity for the dopamine transporter was high as well. These compounds may have utility as medications to treat drug abuse since replacement of the ester with the oxadiazole will produce a compound that is resistant to metabolism and long-lasting.

By producing a series of compounds without the methyl group attached to the nitrogen in the ring structure, we found that demethylation enhanced affinity for the serotonin and norepinephrine transporters between 2- and 44-fold. This will be very useful when trying to design cocaine analogs selective for serotonin and norepinephrine transporters.

A series of amides in the C-2 position were synthesized and tested as well. The results indicated the tertiary amides are more potent at the dopamine transporter than primary and secondary amides. Some of the compounds were both potent and highly selective for the dopamine transporter.

A QSAR and CoMFA study extended knowledge from the structure-activity work and elucidated some features of the cocaine pharmacophore and provided useful predictive information. Additional compounds will be synthesized using this information.

Carroll, F.I., S.W. Mascarella, M.A. Kuzemko, Y. Gao, P. Abranam, A.H. Lewin, J.W. Boja, and M.J. Kuhar. Synthesis, Ligand Binding, and QSAR (CoMFA and Classical) Study of 3b-(4'-Substituted Phenyl)-, and 3b-(3',4'-Disubstituted Phenyl)tropane-2b-carboxylic Acid Methyl Esters. J of Med. Chem., in press.

Carroll, F.I., P. Kotian, J.L. Gray, P. Abraham, M.A. Kuzemko, A.H. Lewin, J.W. Boja, and M.J. Kuhar. 3b-(4Chlorophenyl)tropan-2b-Carboxamides and Cocaine Amide Analogues: New High Affinity and Selective Compounds for the Dopamine Transporter. Med. Chem. Res. 3, 468-472, 1993.

Boja, J.W., M.J. Kuhar, T. Kopajtic, E. Yang, P. Abraham, A.H. Lewin, and F.I. Carroll. Secondary Amine Analogues of 3b-(4'Substituted phenyl)tropane-2b-carboxylic Acid Esters and N-Norcocaine Exhibit Enhanced Affinity for Serotonin and Norepinephrine Transporters. J. Med. Chem. 37, 1220-1223, 1994.

Carroll, F.I., J.L. Gray, P. Abraham, M.A. Kuzemko, A.H. Lewin, J.W. Boja, and M.J. Kuhar. 3-Aryl-2-(3'-Substituted-1',2'4'-oxadiazole-5'yl)tropane analogues of cocaine: Affinities at the cocaine binding site at the dopamine, serotonin, and norepinephrine transporters. J. Med. Chem. 36, 2886-2890, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00112-08 MPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Drug Receptors, Neurotransmitters and Addiction

PRINCIPAL INVESTIGATOR

P.I.	Michael J. Kuhar, Ph.D.	Chief	Neuroscience Branch
	John Boja, Ph.D.	Sr. Staff Fellow	Neuroscience Branch
	Nancy Pilotte, Ph.D.	Staff Fellow	Neuroscience Branch
	Catherine Cerruti, Ph.D.	Visiting Fellow	Neuroscience Branch
	Larry Sharpe, Ph.D.	Pharmacologist	Molecular Neurobiology Branch
	George R. Uhl, M.D., Ph.D	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

F.I. Carroll, Ph.D., Research Triangle Institute

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1.5	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

One focus of this project is to elucidate mechanisms involved in and changes consequent to the long-term, repetitive use of drugs. In one study, we used Lewis rats because they show a greater propensity for self-administering cocaine compared to other strains, treated them with cocaine in a long-term but intermittent fashion and found that there was a decrease in the dopamine transporter at 10 days after withdrawal. The change was not evident at earlier times and a withdrawal period was necessary to generate the change as continuous drug administration for the same amount of time did not result in such a decrease. The decrease in transporter was found in the nucleus accumbens, a limbic area associated with addiction, and not in the striatum, an area associated with motoric function. The decrease in transporter was long lasting and still apparent at 60 days after withdrawal. These long term changes are quite intriguing and suggest very long term changes in the brains of human subjects who are withdrawn from cocaine.

In order to understand the mechanism of this decrease, we tested whether or not there is a decrease in the messenger RNA for the transporter at the time when the transporter was found to be down-regulated. Because only a small number of the dopaminergic neuronal cell groups project to the accumbens, it was necessary to carry out this study as a light microscopic in situ hybridization investigation as it provided the necessary anatomic resolution to identify the various cell groups of dopaminergic-containing neurons. The in situ hybridization studies revealed that there were different levels of messenger RNA for the dopamine transporter in the different cell groups. In drug-treated and withdrawn animals, it was found that there was a significant reduction in mRNA binding levels in the interfascicular nucleus and in the caudal linear nucleus, but not in the other cell groups of the midbrain. These two cell groups that showed a decrease project to the accumbens. Because of the anatomical correspondence between cells showing a decrease in mRNA and nerve terminal fields showing a decrease in transporter binding, we assume a direct connection between the two and suggest that the down regulation in transporter is due to a decrease in expression of the mRNA.

These results indicate that withdrawal from chronic drug administration can result in a series of complicated but long-lasting changes in biochemical parameters in brain. Current directions of this project are aimed at identifying additional proteins or enzymes or transporters that are affected by chronic drug administration.

PUBLICATIONS

Pilotte N.S., Sharpe L.G. and Kuhar M.J. Withdrawal of repeated intermittent intravenous infusions of cocaine results in the delayed reduction of binding to dopamine transporters in the nucleus accumbens of Lewis Rats. JPET, 269, 963-969, 1994.

Cerruti C., Pilotte N.S., Uhl G.R., and Kuhar M.J. Reduction in dopamine transporter mRNA after cessation of repeated cocaine administration. Mol. Brain Research, 22, 132-138, 1994.

Cerruti, C. Walther, D.M., Kuhar, M.J., and Uhl, G.R. Dopamine Transporter mRNA Expression is Intense in Rat Midbrain Neurons and Modest Outside Midbrain. Mol. Brain Research, 18, 181-186, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00118-03 CDM

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Pharmacodynamics of Smoked Drugs of Abuse

PRINCIPAL INVESTIGATOR

P.I.	E.J. Cone	Chief	Clinical Pharmacology Branch
	W.D. Darwin	Chemist	Clinical Pharmacology Branch
	A. Jenkins	IRTA	Clinical Pharmacology Branch
	D. Yousefnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.2	0.8	0.4

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The smoking route is an efficient means of drug delivery. Numerous drugs of abuse are administered by this route including cocaine, marijuana, phencyclidine, heroin and methamphetamine. Methods were developed to study the pharmacokinetics and pharmacodynamics of smoked cocaine and heroin in human volunteer subjects. Healthy subjects with a recent history of abuse of the drug of interest by the smoking route participated in the studies.

Following informed consent, the subjects smoked a low dose of the drug under controlled conditions to assess safety of the procedures. The subjects then participated in a double blind, placebo controlled study of smoked versus intravenous administration of drug. Behavioral and physiological measures and biological samples were collected over time. These data provide important information to our understanding of the pharmacologic actions of these drugs by the smoking route.

Jenkins, A.J., Keenan, R.M., Henningfield, J.E. and Cone, E.J. Pharmacokinetics And Pharmacodynamics Of Smoked Heroin. J. Anal. Toxicol. In Press, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00119-03 CPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Mechanisms of Action of Cocaine

PRINCIPAL INVESTIGATOR

P.I.	Richard Rothman, M.D., P	Chief	Clinical Pharmacology Branch
	David Gorelick, M.D., Ph.	Chief	Treatment Branch
	Steven Goldberg, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Jack Henninfield, Ph.D.	Chief	Clinical Pharmacology Branch
	Jean Cadet, M.D.	Chief	Office of the Director

COOPERATING UNITS

Kenner Rice, Ph.D., John Glowa, Ph.D. NIDDK
Aug Pert, Ph.D, NIMH
F. Ivy Carroll, Research Triangle Institute

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☒ (b) Human Tissue ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK

The Clinical Psychopharmacology Section conducts preclinical and clinical research into the mechanisms of action of cocaine. A major component of this project, conducted in collaboration with investigators at NIDDK and NIMH, is the synthesis and evaluation of analogs of GBR12909 as putative cocaine antagonists or cocaine substitution-type medications. As part of this project, we synthesized and evaluated the first chiral "GBR" derivatives as potent and enantioselective inhibitors of dopamine reuptake. In an extension of previous studies, we showed that daily administration of GBR12909 suppresses cocaine self-administration in Rhesus monkeys without the development of tolerance, supporting its potential use in the treatment of cocaine addiction and that GBR12909 blocks the increase in extracellular DA produced by intravenous cocaine. Another component involves investigation of the possible heterogeneity of DA transporter binding sites. This project has identified multiple and novel binding sites for the high affintiy cocaine analog, [125I]RTI-55. Another component of this project addresses the role of classical conditioning in cocaine-induced behavioral sensitization. These studies demonstrated that associative learning mechanisms are involved in the acquisition of context-specific behavioral sensitization to cocaine. Studies with genetically inbred strains of mice showed that the occurrence of sensitization is not correlated with either the potency or efficacy of cocaine as a motoric stimulant. Human studies failed to demonstrate cocaine-sensitization with a one day training paradigm (IRP-174). Open-label studies with phentermine and fenfluramine showed that these medications suppress cocaine craving in addicts seeking treatment. Clinical research protocols are in preparation to determine the efficacy of fenfluramine and phentermine as treatments for alcohol and cocaine addiction.

Dersch, C. M., H. C. Akunne, J. S. Partilla, G. U. Char, B. R. de Costa, K. C. Rice, F. I. Carroll, and R. B. Rothman (1993). Studies of the biogenic amine transporters. I. dopamine reuptake blockers inhibit [3H]mazindol binding to the dopamine transporter by a competitive mechanism: preliminary evidence for different binding domains. Neurochem. Res., 19(2):201-208.

Rothman, R. B., K. M. Becketts, L. R. Radesca, B. R. de Costa, K. C. Rice, F. Ivy Carroll, and C. M. Dersch (1993). Studies of the biogenic amine transporters. II. a brief study on the use of [3H]-DA-uptake-inhibition to transporter-binding-inhibition ratios for the in vitro evaluation of putative cocaine antagonists.

Baumann, M. H., A. M. Brockington, and R. B. Rothman (1993). Withdrawal from chronic cocaine enhances behavioral sensitivity to the 5-HT2/1C agonist DOI. Biol. Psychiatry, 34:576-577.

Baumann, M. H., J. J. Rutter, and S. B. Auerbach (1993). Intravenous administration of the serotonin agonist m-chlorophenylpiperazine (mCPP) increases extracellular serotonin in the diencephalon of awake rats. Neuropharmacology, 32(12):1381-1386.

Cadet, J. L., P. Sheng, S. Ali, R.B. Rothman, E. Carlson, and C. Epstein (1994). Attenuation of methamphetamine-induced neurotoxicity in copper/zinc superoxide dismutase transgenic mice. J. Neurochem., 62(No. 1):380-383.

Akunne, H. C., C. M. Dersch, J. L. Cadet, M. H. Baumann, G. U. Char, J. S. Partilla, B. R. de Costa, K. C. Rice, F. I. Carroll, and R. B. Rothman (1994). Studies of the biogenic amine transporters. III. demonstration of two binding sites for [3H]GBR12935 and [3H]BTCP in rat caudate membranes. J. Pharmacol. Exp. Ther., 268 (No.3):1462-1475

Baumann, M. H., J. L. Cadet, P. L. Sheng, and R. B. Rothman (1994). Evidence for alterations in 5-HT2/1C receptor sensitivity after repeated cocaine injections. Problems of Drug Dependence 1993. NIDA Res. Monogr., 141:126.

Becketts, K. M., M. S. Silverthorn, J. L. Cadet, C. M. Dersch, J. S. Partilla, B. R. de Costa, K. C. Rice, L. Radesca, F. I. Carroll and R. B. Rothman (1994). Resolution of two serotonin transporter-related binding sites with the cocaine analog, [125I]RTI-55. NIDA Res. Monogr., 141:324.

Brockington, A., R. B. Rothman, D. Gorelick, S. R. Goldberg, and G. I. Elmer (1994). Genetic factors in acute cocaine-induced locomotor activity and context-specific conditioned sensitization. NIDA Res. Monogr., 141:16.

Cadet, J. L., T. Gendron, W. R. Lange, J. E. Henningfield, and R. B. Rothman (1994). The clinical neurological examination in chronic cocaine abusers: preliminary findings. NIDA Res. Monogr., 141:31.

Char, G. U., M. H. Baumann, C. I.-T. Chen, K. C. Rice, B. R. de Costa, D. Matecka, and R. B. Rothman (1994). The cocaine-induced rise in extracellular dopamine in the nucleus accumbens is reduced by GBR-12909 pretreatment. NIDA Res. Monogr., 141:122.

Dersch, C., J. L. Cadet, J. S. Partilla, B. R. de Costa, K. C. Rice, F. I. Carroll, H. A. Akunne, and R. B. Rothman (1994). Demonstration of multiple binding sites in rat caudate membranes for the cocaine analog [125I]RTI-55. NIDA Res. Monogr., 141:125.

Gendron, T., R. B. Rothman, J. L. Cadet, B. S. Koeppl, D. A. Gorelick, J. E. Henningfield, and W. B. Pickworth (1994). Possible conditioning effects of intravenous cocaine on pupillary diameter. NIDA Res. Monogr., 141:313.

Glowa, J. R., F. H. Wojnicki, B. de Costa, D. Matecka, K. C. Rice and R. B. Rothman (1994). The effects of GBR 12909 on responding of rhesus monkeys maintained under schedules of cocaine- and food-delivery. NIDA Res. Monogr., 141:12.

Matecka D., B. R. de Costa, R. B. Rothman, M. L. Silverthorn, L. Radesca, C. M. Dersch, K. M. Becketts, A. Pert, J. Glowa, and K. C. Rice (1994). Synthesis and evaluation of the first chiral "GBR" derivatives as potent

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00120-03 CPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Characterization of Anti-Opioid Peptides in Opioid Tolerance and Dependence

PRINCIPAL INVESTIGATOR

P.I.	Richard Rothman, M.D., P	Chief	Clinical Pharmacology Brancn
	Heng Xu, Ph.D.	Visiting Scientist	Clinical Pharmacology Brancn
	Carl Goodman, Ph.D.	IRTA	Clinical Pharmacology Branch
	Michael Buaman, Ph.D.	Staff Fellow	Clinical Pharmacology Branch
	Jean Cadet, M.D.	Chief	Neuroscience Branch

COOPERATING UNITS

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Clinical Pharmacology Branch

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Clinical Psychopharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	3	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☒ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

The CNS synthesizes and secretes several neuropeptides which attenuate the actions of morphine including CCK-8, Tyr-MIF, Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH2 (NPFF), alpha-MSH and dynorphin(1-17). The anti-opioid model of tolerance and dependence postulates that administration of morphine produces increased secretion of anti-opioids, which attenuate the effects of morphine, and thereby maintain a homeostatic balance. A prediction of the anti-opioid model is that administration of an anti-opioid should attenuate the development of tolerance and dependence. A major finding of this project is that administration of anti-NPFF IgG to dependent rats attenuates naloxone-induced withdrawal. In addition, recent autoradiographic studies have shown that the density of the opioid mu receptor in the brain is under tonic inhibitory control by NPFF. Importantly, the mu receptors in the mesolimbic system are regulated by NPFF. Preliminary studies indicate that NPFF antagonizes the reinforcing effects of morphine. Heroin addicts suffer from dysphoric mood states prior to and during their addiction, as well as during periods of abstinence. One hypothesis to explain this is increased levels of dynorphin, which, via activation of kappa opioid receptors, produces dysphoria. This hypothesis is being tested in the clinical protocol: Anti-opioid peptide levels in the plasma and CSF of drug abusers and age matched controls (IRP-192). We continue our collaborations with medicinal chemists to identify potent and selective kappa antagonists. The significance of this project to drug abuse reselRPh is that the delineation of novel mechanisms involved in opioid tolerance and dependence will eventually lead to novel, and more specific treatments for addiction.

Rothman, R. B., L. S. Brady, H. Xu, and J. B. Long (1993). Chronic Intracerebroventricular infusion of the anti-opioid peptide, Phe-Leu-Phe-Gin-Pro-Gin-Arg-Phe-NH2(NPFF), down-regulates mu opioid binding sites in rat brain. Peptides, 14:1271-1277.

Goodman, C. B., J. L. Cadet, M. H. Baumann, H.-Y. T. Yang, C.-H. Lee, and R. B. Rothman (1994). Modulation of opioid mu receptor density by the endogenous anti-opioid peptide, NPFF. NIDA Res. Monogr., 141:307.

Partilla, J., J. You and R. B. Rothman (1994). Isolation of opiate and "anti-opiate" peptides from human plasma. NIDA Res. Monogr., 141:308.

Raffa, R. B., A. Kim, K. C. Rice, B. R. de Costa, E. E. Codd, and R. B. Rothman (1994). Low affinity of FMRFamide and four FaRPs (FMRFamide-related peptides), including the mammalian-derived F-8-Famide (NPFF) and A-18-Famide, for opioid m,d ,k1 ,k2a or k2b receptors. Peptides, 15(No.3):401-404.

Goodman, C. G., G. I. Elmer, H-Y. T. Yang, C. H. Lee, and R. B. Rothman (1994). Modulation of opioid receptors by anti-opioid peptides. In Pharmacology of Opioid Peptides, Harwood Academic Publishers, GMBH, in press.

Goodman, C. B., J. L. Cadet, B. Emilien, and R. B. Rothman (1994). Down-regulation of mu opioid binding sites following continuous ICV infusion of NPFF and morphine: an autoradiographic study. NIDA Res. Monogr., in press.

Goodman, C. B., B. Emilien, J. L. Cadet, and R. B. Rothman (1994). Chronic ICV infusion of morphine and NPFF down-regulate mu opioid receptors in rat brain: a quantitative autoradiographic study. Regulatory Peptides, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00121-04 CPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Structure And Function of the Opioid Receptor/Endorphin System

PRINCIPAL INVESTIGATOR

P.I.	Richard Rothman, M.D., P	Chief	Clinical Pharmacology Branch
	Heng Xu, Ph.D.	Visiting Scientist	Clinical Pharmacology Branch
	Qi Ni, Ph.D.	Visiting Fellow	Clinical Pharmacology Branch
	Y. Cha, Ph.D.	Visiting Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

Kenner Rice, Ph.D., NIDDK
F. Ivy Carroll, Ph.D, Reserach Triangle Institute

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Clinical Psychopharmacology

INSTITUTE AND LOCATION

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TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	3	0

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☒ (A) Human ☒ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

The unambiguous demonstration of opioid receptor types, and their endogenous ligands, the endorphins, together with a diverse range of synthetic ligands, has created exciting opportunities for research highly relevant to drug abuse. A major objective of this project is to continue the process of defining new opioid receptor subtypes. This process is optimally accomplished by synergistic collaborations with medicinal chemists to develop (a) selective high affinity ligands for each subtype (b) irreversible ligands with receptor subtype specificity and (c) enantiomeric pairs of these ligands for detection of receptor mediated effects. Delta receptor antagonists attenuate alcohol consumption and block morphine tolerance and dependence. The CPS is a leading lab in the determination of delta receptor subtypes.: recent studies demonstrated two subtypes of the delta-ncx binding site, and provided new information about subtypes of the delta-cx subtype. The determination of delta receptor subtypes may lead to new medicines for the treatment of alcoholism and drug addiction. Converging lines of investigation suggest that kappa receptor antagonists may be useful for the treatment of depression, anxiety, psychosis and craving. Studies reported last year demonstrated up to four subtypes of kappa opioid receptors in rat, guinea pig and human brain, suggesting that it may be possible to develop kappa agonists devoid of psychotomimetic side effects. More recent studies have resolved yet more kappa receptor subtypes. Investigations carried out with highly potent analogs of (+)-cis-3-methylfentanyl have identified analogs over 100,000 x the antinociceptive potency of morphine and allowed us to determine the stereochemical requirements of pseudoirreversible inhibition. These drugs provide unique information about the topography of the mu receptor binding site, and interact with the mu receptor according to a pseudoallosteric mechanism. The notion that dysfunction of the CNS opioid receptor/endorphin system underlies certain mental illnesses, and contributes to drug abuse, remains a viable, but unproved, hypotheses

Xu, H., J. S. Partilla, B. R. de Costa, K. C. Rice, and R. B. Rothman (1993). Differential binding of opioid peptides and other drugs to two subtypes of opioid dncx binding sites in mouse brain: further evidence for d receptor Heterogeneity. Peptides, 14:893-907.

Ni, Q., H. Xu, J. S. Partilla, P. A. Stark, F. I. Carroll, G. A. Brine, and R. B. Rothman (1993). Stereochemical requirements for pseudoirreversible inhibition of opioid mu receptor binding by the 3-Methylfentanyl congeners, RTI-46144 and its enantiomers: evidence for different binding domains. Synapse, 15:296-306.

Ni, Q., H. Xu, J. S. Partilla, B. R. de Costa, K. C. Rice, and R. B. Rothman (1993). Selective labeling of kappa2A opioid receptors in rat brain by [125I]IOXY: interaction of opioid peptides and other drugs with multiple kappa2A binding sites. Peptides, 14:1279-1293.

Bertha, C. M., J. Flippen-Anderson, R. B. Rothman, H. Xu, X. Y. Cha, A. E. Jacobson, and K. C. Rice (1994). Indolo-5-arylmorphans as potential selective opioid receptor probes. NIDA Res. Monogr., 141:49.

Calderon, S. N., C. George, H. Xu, X. Y. Cha, R. B. Rothman, K. D. Wild, E. J. Bilsky, F. Porreca, A. E. Jacobson, and K. C. Rice (1994). Synthesis and absolute configuration of optically pure enantiomers of (+)-BW373U86. Development of SNC80, a potent and selective nonpeptidic d-opioid receptor agonist. NIDA Res. Monogr., 141:257.

Cha, X. Y., H. Xu, C.-H. Kim, K. C. Rice, and R. B. Rothman (1994). Probing the opioid receptor complex with (+)-trans-superfit: resolution of two dcx binding sites. NIDA Res. Monogr., 141:238.

Ni, Q., H. Xu, J. S. Partilla, B. R. de Costa, K. C. Rice, and R. B. Rothman (1994). Resolution of kappa2a opioid receptor subtypes in rat brain using [125I]IOXY. NIDA Res. Monogr., 141:239.

Xu, H., J. S. Partilla, B. R. de Costa, K. C. Rice, and R. B. Rothman (1994). Differential binding of opioid peptides and other drugs to two subtypes of opioid dncx binding sites in mouse brain: further evidence for d receptor heterogeneity. NIDA Res. Monogr., 141:237.

Lai, J., E. J. Bilsky, R. B. Rothman, and F. Porreca (1994). Treatment with antisense oligodeoxynucleotide to the opioid d receptor selectively inhibits d2-agonist antinociception. NeuroReport, 5:1049-1052.

Ni, Q., H. Xu, J. S. Partilla, B. R. de Costa, K. C. Rice, A. Borsodi, S. Hosztafi, and R. B. Rothman (1994). Dihydrocodeinone-hydrazone, dihydrocodeinone-oxime, naloxone-3-ome-oxime, and clocinnamox fail to irreversibly inhibit opioid kappa receptor binding. Neurochem. Res., in press.

Rothman, R. B., Q. Ni, and H. Xu (1994). Buprenorphine: a review of the binding literature. In: Buprenorphine: Combatting Drug Abuse With a Unique Opioid, A. Cowan and J. W. Lewis (eds), John Wiley & Sons, Inc., New York, in press.

Calderon, S. N., R. B. Rothman, F. Porreca, J. Flippen-Anderson, R. W. McNutt, H.Xu, L. E. Smith, E. J. Bilsky, P. Davis, and K. C. Rice (1994). Probes for narcotic receptor mediated phenomena. 191. Synthesis of (+)-4-[(aR)-a((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-m ethoxybenzyl]-N,N-diethylbenzamide (SNC 80): a highly selective, nonpeptide delta opioid receptor agonist. J Med. Chem., in press.

Porreca, F., R. N. Bernstein, S. N. Calderon, K. C. Rice, R. B. Rothman, and E. J. Bilsky (1994). Antinociceptive profile of SNC80, a highly selective, non-peptidic delta opioid agonist. NIDA Res. Monogr., in press.

Cha, X. Y., H. Xu, S. N. Calderon, K. C. Rice, F. Porreca, and R. B. Rothman (1994). The non-peptide delta agonist, BW373U86, its enantiomers, and related compounds: interactions at multiple dcx binding sites in rat brain. NIDA Res. Monogr., in press.

Kayakiri, H., R. B. Rothman, H. Xu, J. S. Partilla, and K. C. Rice (1994). Synthesis and biological evaluation of 6b- and 6a-IODO-3,14-dihydroxy-17-methyl-4,5a-epoxymorphinans. NIDA Res. Monogr., in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00122-03 CPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Characterization of PCP and sigma receptors

PRINCIPAL INVESTIGATOR

P.I. Richard Rothman, M.D., P Chief — Clinical Pharmacology Branch

Carl Goodman, Ph.D. IRTA — Clinical Pharmacology Branch

COOPERATING UNITS

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TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	3	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Phencyclidine (PCP) and sigma receptors, though linked in terms of their historical development, and their generally high affinity interactions with (+)-opiates, are now known to be pharmacologically and biochemically distinct binding sites. The PCP binding site, because it is but one component of the NMDA receptor, is relevant to drug abuse research because the NMDA receptor plays important roles in neuronal processes involved in substance abuse, such as memory, propagation of seizures and kindling, tolerance and dependence. Previous studies showed that the PCP analog, [3H]TCP labels two high affinity PCP binding sites: PCP site 1 (NMDA-receptor-associated) and PCP site 2 (biogenic-amine -transporter-associated). Collaborative investigations with F. Ivy Carroll lead to the discovery of RTI-4793-14, which has high potency and selectivity for PCP site 2. This novel pyrole has a neurochemical profile consistent with that of an antidepressant. A patent application on this compound was filed. More recent PCP site 2 ligands show promise as potential anti-craving medications.

Carroll, F. I., B. E. Blough, S. W. Mascarella, H. Xu, C. B. Goodman, and R. B. Rothman (1993). Synthesis and ligand binding at PCP sites 1 and 2 for hexahydro-2-substituted-1-methylindeno[1,2-b]pyrroles. Med. Chem. Res., 3:178-182.

Goodman, C. B., D . N. Thomas, A. Pert, B. Emilien, J. L. Cadet, F. I. Carroll, B. E. Blough, S. W. Mascarella, M. A. Rogawski, S. Subramaniam, and R. B. Rothman (1994). RTI-4793-14, a new ligand with high affinity and selectivity for the (+)-MK-801-insensitive [3H]1-[1-(2-thienyl)cyclohexyl]piperi dine binding site (PCP Site 2) of guinea pig brain. Synapse, 16:59-65.

Akunne, H. C., J. A. Monn, A. Thurkauf, A. E. Jacobson, K. C. Rice, J. T. M. Linders, Q. Jiang, F. Porreca, and R. B. Rothman (1994). An electrophilic affinity ligand based on (+)-MK801 distinguishes PCP site 1 from PCP site 2. Neurochem. Res., 19 (No.4):385-389.

Emilien, B., C. B. Goodman, F. I. Carroll, B. Blough, M. A. Rogawski, S. Subramaniam, and R. B. Rothman (1994). RTI4793-14: a new ligand with high affinity and selectivity for PCP site 2. NIDA Res. Monogr., 141:311.

DiCesare, J. C., J. P. Burgess, S. W. Mascarella, F. I. Carroll, and R. B. Rothman (1994). Synthesis and structural determination of 5H-benzocyclohepten-5,8-imines. J. Heterocyclic Chem., 31:187-192.

30. Rothman, R. B. (1994). PCP Site 2: a high affinity MK801-insensitive phencyclidine binding site. Neurotoxicol. Teratol., 16(No.4):343-353.

Goodman, C. B., B. Emilien, C. M. Dersch, J. S. Partilla, J. L. Cadet, D. J. Vandenbergh, J.-B. Wang, G. R. Uhl, F. I. Carroll, B. Blough, K. P. Constable, and R. B. Rothman (1994). Discovery of a novel chiral benzazepine derivative, RTI-4793-41, whose enantiomers bind potently and with moderate enantioselectivity to PCP site 2 and cloned DA transporters. NIDA Res. Monogr., in press.

Bertha, C. M., M. V. Mattson, J. L. Flippen-Anderson, R. B. Rothman, H. Xu, X-Y. Cha, K. Becketts, and K. C. Rice (1994). A marked change of receptor affinity of the 2-methyl-5-(3-hydroxyphenyl)morphans upon attachment of an E-8-benzylidene moiety: the synthesis and evaluation of a new class of s receptor ligands. J. Med. Chem., in press.

Bertha, C. M., C. Mattson, C. George, R. B. Rothman, H. Xu, X.-Y. Cha, K. Becketts, and K. C. Rice (1994). Introduction of an _-8-benzylidene moiety in the 2-methyl-5-phenylmorphan system abolishes opioid effects and affords a new class of potent sigma receptor ligands. NIDA Res. Monogr., in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00200-09 NDAS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Brain Imaging Studies of Drug Abuse

PRINCIPAL INVESTIGATOR

P.I.	E.D. London, Ph.D.	Chief	Neuroscience Branch
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	S.J. Grant, Ph.D.	Sr. Staff Fellow	Neuroscience Branch
	V. Villemagne, M.D.	Visiting Associate	Neuroscience Branch
	X. Liu, Ph.D.	Visiting Fellow	Neuroscience Branch
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COOPERATING UNITS

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Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
5.6	5.6	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Noninvasive brain imaging is used to study biological correlates of drug abuse in human volunteers. Positron emission tomography (PET) and electroencephalography (EEG) show that euphoriants reduce global and regional cerebral metabolic rates for glucose (CMRglc, rCMRglc), and increase a power. Changes in rCMRglc induced by morphine or cocaine and in EEG a power produced by morphine are correlated with positive affect. Cocaine-induced changes in rCMRglc but not in b power are related to mood. Buprenorphine, a mixed opioid agonist/antagonist, decreases regional CMRglc (rCMRglc), as do other abused drugs, such as morphine, cocaine, and nicotine. In subjects with histories of cocaine abuse, ongoing studies suggest that cocaine-related stimuli produce drug craving, arousal (desynchronization of a activity), and increased rCMRglc in areas of the limbic system. Patients with acquired immunodeficiency syndrome (AIDS) show metabolic defects in the limbic system, consistent with an involvement of the hippocampus and related areas in cognitive deficits associated with AIDS dementia. Drug abusers that are seronegative for human immunodeficiency virus manifest lower rCMRglc in visual association cortex and higher rCMRglc in orbitofrontal cortex than non-drug abusing controls matched for age and socioeconomic status. To determine whether these differences predate or result from drug abuse, rCMRglc and regional cerebral blood flow are studied in twins discordant for drug abuse. Magnetic resonance imaging is used to study brain structure, as related to personality and cognition in substance abusers. Volumetric analyses reveal no evidence of ventriculomegaly in substance abusers who are otherwise healthy. Ongoing studies assess potential differences in structure of the orbitofrontal cortex, a brain region that shows a difference in rCMRglc in drug abusers as compared to controls. Studies in newborn sheep assessed the effects of cocaine on cerebral blood flow (CBF). A single dose of cocaine almost doubled CBF at 30 s while arterial blood pressure was increased; CBF returned to control within 5 min. In sheep that received cocaine repeatedly, CBF 30 s after the fifth dose was stimulated as after the first, and remained elevated for 1 h. Cerebral vasodilation, combined with hypertension, may contribute to cocaine-associated neonatal neurologic damage. An improved form of a model for calculation of (CMRglc) from PET data has been developed to obviate the need for arterial blood samples or any blood samples collected early after injection of the radiotracer.

PUBLICATIONS

Morgan MJ, Cascella NG, Stapleton JM, Phillips RL, Yung BCK, Wong DF, Shaya EK, London ED. Sensitivity to subjective effects of cocaine in drug abusers: Relation to cerebral ventricular size, Am J Psychiatry 1993;150:1712-1717.

ED London. Seeing the brain: The role of PET, autoradiography, and other imaging techniques. In: Biomedical Approaches to Illicit Drug Demand Reduction, Hartel CR, ed. Proceedings of the International Research Conference, Georgia: NIDA, NIH publication no. 03-3698, 1993:235-241.

O'Brien TP, Gleason CA, Jones MD Jr, Cone EJ, London ED, Traystman RJ. Cerebral responses to single and multiple cocaine injections in newborn sheep, Pediatr Res 1994;35:339-343.

London ED. Positron emission tomography in studies of drug abuse, NIDA Res Monogr 1994;138:15-24.

Walsh SL, Gilson SF, Jasinski DR, Stapleton JM, Phillips RL, Dannals RF, Schmidt J, Preston KL, Grayson R, Bigelow GE, Sullivan JT, Contoreggi C, London ED. Buprenorphine reduces cerebral glucose metabolism in polydrug abusers, Neuropsychopharmacology 1994;10:157-170.

Phillips RL, Herning R, London ED. Morphine effects on the spontaneous electroencephalogram in polydrug abusers: Correlations with subjective self-reports, Neuropsychopharmacology 1994;10:171-181.

Stapleton JM , London ED. Imaging techniques, Encycl Drugs & Alcohol, in press.

Herning RI, Glover BJ, Koeppl B, Phillips RL, London ED. Cocaine-induced increases in EEG alpha and beta activity evidence for reduced cortical processing, Neuropsychopharmacology, in press.

London ED. Patterns of nicotine action in the brain, Tobacco Control, in press.

Newlin DB, Pretorius MB, Wong CJ, Stapleton JM, London ED. Acute intravenous cocaine educes cardiac vagal tone in cocaine abusers, NIDA Res Monogr, in press.

Phillips RL, Chen CY, Wong DF, London ED. An improved method to calculate metabolic rates for glucose using PET, J Nucl Med, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00202-11 NDAS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Physiological Effects of Opioids

PRINCIPAL INVESTIGATOR

P.I.	E.D. London	Chief	Neuroscience Branch
	J.A. Bell	Pharmacologist	Neuroscience Branch
	A.S. Kimes	Biologist	Neuroscience Branch
	D.B. Vaupel	Pharmacologist	Neuroscience Branch
	S.J. Grant	Sr. Staff Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.55	2.55	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

In vitro, animal and human studies are performed to elucidate mechanisms of opioid action and to develop new modalities for treating opioid addiction. Chronic morphine treatment produces dependence and tolerance as demonstrated in electrophysiological assays of synaptic activity in the isolated spinal cord from neonatal rats. Chemically and electrically evoked responses of nociceptive neurons show opioid tolerance that is not prevented by co-treatment with dizocilpine. Based upon studies in slices of rat brain, that show inhibition of nitric oxide synthase (NOS) diminishes the development of tolerance to morphine in noradrenergic neurons of the locus ceruleus (LC) of adult morphine-treated rats, new studies in intact anesthetized rats investigate the role of LC as a cellular substrate for the involvement of nitric oxide in opioid withdrawal. New behavioral experiments demonstrate that various NOS inhibitors consistently reduce certain withdrawal signs in the rat, and yield pharmacological profiles similar to that of clonidine. 7-Nitroindazole (7-NI), a NOS inhibitor specific for cerebral NOS, attenuates more withdrawal signs than other NOS inhibitors. Further, 7-NI lacks the vasopressor activity common to other NOS inhibitors, suggesting that 7-NI holds promise as a possible treatment for opioid addiction in humans. Other work in rats shows that behavioral signs of opioid withdrawal and widespread stimulation of cerebral glucose metabolism occur when methylnaloxonium, a quaternary opioid antagonist, is injected directly into LC of morphine-dependent rats. The findings demonstrate that increased metabolic activity in regions of the brain when withdrawal is precipitated by peripheral opioid antagonist administration is most likely due at least in part to stimulation of the LC. In drug-naive rats, buprenorphine mimics the effect of morphine on cell firing, but in morphine-dependent rats buprenorphine mimics naloxone, consistent with the hypothesis that the actions of buprenorphine, a partial opioid agonist, vary with the state of opioid dependence. An assessment in human volunteers of the interactions of the calcium channel antagonist verapamil with morphine shows that verapamil antagonizes the positive affective changes produced by morphine and potentiates the analgesic effects of morphine.

PUBLICATIONS

Kimes AS, Vaupel DB, London ED. Nitric oxide in opioid withdrawal: Attenuation of some withdrawal signs by inhibitors of nitric oxide synthase, Psychopharmacology (Berl) 1993;112:521-524.

Vaupel DB, Lange WR, London ED. Effects of verapamil on morphine-induced subjective effects, analgesia and respiratory depression in humans, J Pharmacol Exp Ther 1993;267:1386-1394.

Vaupel DB, Lange WR, London ED. Verapamil potentiates morphine analgesia and reduces euphoria in human subjects, NIDA Res Monogr, in press.

London ED, Kimes AS, Vaupel DB. Inhibitors of nitric oxide synthase and the opioid withdrawal syndrome, NIDA Res Monogr, in press.

Vaupel DB, Kimes AS, London ED. Comparison of 7-nitroindazole with other nitric oxide synthase inhibitors as attenuators of opioid withdrawal, Psychopharmacology, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00206-09 MPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Biological and Biochemical Characterization of Sigma Receptors

PRINCIPAL INVESTIGATOR

P.I.	T.P.Su, Ph.D.	Research Chemist	Neuroscience Branch
	S. Yu, Ph.D.	Visiting Fellow	Neuroscience Branch
	L.I. Tsao, Ph.D.	Staff Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.9	2.9	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project delineates biochemical, chemical, and pharmacological properties of sigma receptors and ligands. Sigma ligands are examined for a modulation of the NMDA receptor complex-mediated learning processes. Learning capacities are evaluated using the spontaneous alternation in a Y-maze test for spatial working memory, and the step-down passive avoidance and the elevated plus-maze test for long-term memory. PRE-084, a selective sigma ligand discovered at this laboratory, attenuate MK-801-induced impairment of memory processes in all three tests. These effects of PRE-084 are antagonized by a sigma receptor antagonist BMY-14802. Solubilized sigma receptors are partially purified using anion-exchange and hydrophobic interaction chromatographies. Throughout the chromatographic procedures, a chromophore with a strong absorbance at 415 nm co-migrates with sigma receptors. The result suggests that sigma receptors may have a close relationship with a chromophore. Further purification of the receptors is underway.

Su T-P (1993): Delineating biochemical and functional properties of s receptors: Emerging concept. CRC Critical Reviews in Neurobiology, 7:187-203.

Weissman AD, DJ McCann, JF Lorden and T-P Su (1993): An absence of changes in sigma receptor subtypes in the brains of genetically dystonic (dt) rats. Eur. J. Pharmacol., 250:329- 332.

Su T-P and JL Junien (1994): Sigma receptors in the central nervous system and the periphery. In: The Sigma Receptors, Ed. Y Itzhak, pp. 21-44, Academic Press, London.

McCann DJ, AD Weissman and T-P Su (1994): Sigma1 and sigma2 sites in rat brain: Comparison of regional, ontogenetic, and subcellular patterns. Synapse, 17:182-189.

Calderon, SN, S Izenwasser, B Heller, JS Gutkind, M Mattson, T.-P. Su and AH Newman (1994): Novel 1-phenylcycloalkanecarboxylic acid derivatives are potent and selective sigma1 ligands. J. Med. Chem., in press.

Maurice T, T-P Su, DW Parish and A Privat (1994): PRE-084, a s selective PCP derivative, attenuates MK-801-induced impairment of learning in mice. Pharmacol. Biochem. Behav., in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00225-02 GS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Genetic Approaches to Charaterizing Drug Responses and Vulnerabilities

PRINCIPAL INVESTIGATOR

P.I.	Rodney Marley, Ph.D.	Sr. Staff Fellow	Molecular Neurobiology Branch
	Lucinda Miner, Ph.D.	Sr. Staff Fellow	Molecular Neurobiology Branch
	Nancy Goodman	Pharmacologist	Molecular Neurobiology Branch
	Kazuaki Shimosato, Ph.D.	Visiting Fellow	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Genetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	0	2.49

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

There are large individual differences among humans and animals in behavioral, physiological and toxicological responses to drugs of abuse. These individual differences in behavioral responses to drugs also display substantial genetic and environmental influences, are continuously distributed, and appear to be influenced by many genes rather than one or two major genes. For these reasons, application of several of the techniques of genetics and molecular biology could be helpful in identification of genetic influences in readily-studied experimental animals that could shed light on human interindividual differences, and identify genes potentially responsible for behavioral variation in drug responses in these animals.

Differences between several inbred mouse strains' normal responses to psychomotor stimulants and "kindling" induced by repetitive drug administration have been sought and correlated with strain-to-strain differences in biochemical parameters related to opiate receptor, GABAA receptor, and dopamine transporter densities and/or function. Recombinant inbred strains have been tested for cocaine-induced locomotor responses and sensitization. Animals from a heterogenous stock have been tested for cocaine-induced locomotor activation, and have been used to establish a genetic selection paradigm to ask if selection for cocaine-induced locomotion also selects for other cocaine-induced functions, including psychomotor stimulant conditioned place preference measures. Each of these approaches will allow improved assessment of genetic influences in substance abuse, and analyses of the recombinant inbred strain comparisons will allow chromosomal mapping of specific genes contributing to the strain differences through quantitative trait locus approaches.

Miner LL, Elmer GI, Pieper JO, Marley RJ. Aggression modulates genetic influences on morphine analgesia as assessed using a classical Mendelian cross analysis. Psychopharmacology 1993;111:17-22.

Marley RJ, Shimosato K, Frieman M, Goldberg SR. Time course for the development and persistence of the anticonvulsant effects of carbamazepine against cocaine seizures in three strains of mice, Brain Res. 1993;600:193-200.

Marley RJ, Collins AC, Elmer GI, Sudakov SK, Belknap J, McClearn GE, Pickens RW, Goldberg SR. Genetic approaches to understanding the actions of drugs of abuse. In: Problems of drug dependence 1992: Proceedings of the 54th Annual Scientific Meeting of the College on Problems of Drug Dependence 1992;NIDA Res Mongr 1993;132:47-51.

Sannerud CA, Marley RJ, Serdikoff SL, Alastra AJG, Cohen C, Goldberg SR. Tolerance to the behavioral effects of chlordiazepoxide: Pharmacological and biochemical selectivity, J Pharmacol Exp Ther 1994;267:1311-20.

Marley RJ, Shimosato K, Elmer GI, Miner LL. Pharmacogenetic approaches to drug dependence. In: Wonnacott S, Lunt GG, eds. Biochemistry of Drug Dependence. London: Portland Press, 59:153-172, 1993.

Gewiss M, Marley RJ, Thorndike EB, Goldberg SR, Schindler CW. GABA-receptor linked chloride channels and the behavioral effects of naltrexone in rats, Pharmacol Biochem Behav 1994;in press.

Miner LL, Marley RJ. Chromosomal mapping of loci influencing sensitivity to cocaine-induced seizures in BXD Recombinant Inbred strains of mice, Psychopharmacol 1994;in press.

Shimosato K., Saito T, Marley RJ. Genotype specific blockade of cocaine-induced weight loss by the protein synthesis inhibitor, anisomycin, Life Sci 1994;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00226-03 MPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Cocaine Receptor: Biochemical and Molecular Studies

PRINCIPAL INVESTIGATOR

P.I.	Michael J. Kuhar, Ph.D.	Chief	Neuroscience Branch
	Amral Patel, Ph.D.	Sr. Staff Fellow	Neuroscience Branch
	Roxanne Vaughan, Ph.D.	Visiting Fellow	Neuroscience Branch
	Catherine Cerruit	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4	3	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The goal of this project is to elucidate the nature of the dopamine transporter, a key cocaine receptor, in terms of its function and as a protein. The characterization of this protein as a cocaine binding site and as an entity of the dopaminergic neuron is essential in understanding its function.

One of the key findings about the dopamine transporter is that there appear to be different post-translationally modified forms, at least with regard to its molecular weight. The differences in molecular weight appear to be due at least in part to changes in glycosylation, although it is not possible to rule out other sources of heterogeneity as well. In a recent study, we have found that over development and aging, the molecular weight of the dopamine transporter changes. Again, a significant part of this change is due to differences in glycosylation. These results indicate that if dopaminergic neurons are used from immature species, for example for transplant, the transporter is not the same as that in the fully developed adult.

The mechanisms that regulate the dopamine transporter are not fully understood. Because of the new knowledge that glutamatergic synapses result in the elaboration of nitric oxide, and because dopaminergic synapses have been found adjacent to glutamatergic synapses in striatal tissue, we tested whether or not nitric oxide would inhibit dopamine uptake. We found that nitric oxide inhibits dopamine uptake in a time, dose and temperature dependent fashion. The inhibition of dopamine uptake occurs at lower concentrations of nitric oxide generator than does the inhibition of glutamate uptake. These are the first demonstrations that nitric oxide affects neurotransmitter uptake and could have profound implications in the way dopamine transport is regulated. The next goal is to show that this regulation occurs in vivo.

Primary cell cultures of embryonic rat mid-brain cells can be used to study the transporter with certain advantages. Since it is clear that these cells are not within the brain, we wanted to test whether or not the dopamine transporter in these primary cultures was similar to that in mature rat brain at least, in regard to their pharmacology. We found that cocaine analogs inhibited dopamine uptake in these cultures in a fashion that did not differ from that in adult rat brain. We also showed that the solubilized dopamine transporter can readily be studied by standard receptor binding techniques. This will facilitate a variety of experiments.

We continue to make substantial progress in understanding the nature of the dopamine transporter protein, how it is processed and possible mechanisms for its regulation.

Brouard A, Pelaprat D, Boja JW, Carroll FI, Vial M. Kuhar MJ, Rostene W. Potent cocaine Analogs, Inhibit [3H]Dopamine Uptake in Rat Mesencephalic Cells in Primary Cultures: Pharmacological Selectivity of Embryonic Cocaine Sites. Dev. Brain Research, 75, 13-17, 1993

Patel, A. Characterization of [125]RTI-55 Binding to Dog Caudate Dopamine Transporter. Neuroreport, 5, 157-160, 1993.

Patel, A.P., Cerruti, C., Vaughan, R.A., and Kuhar, M.J. Developmentally Regulated Glycosylation of Dopamine Transporter. Dev. Brain Research, in press.

Pogun, S., Baumann, M.H., and Kuhar, M.J. Nitric Oxide Inhibits [3H] Dopamine Uptake. Brain Research 641, 83-91, 1994.

Pogun, S., Dawson, V. and Kuhar, M.J. Nitric Oxide Inhibits 3H-Glutamate Transport in Synaptosomes. Synapse, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00227-02 MNP

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Clinical Neurological Examination in Cocaine Abusers

PRINCIPAL INVESTIGATOR

P.I.	Jean Lud Cadet, M.D.	Chief	Neuroscience Branch
	W.R. Lange, M.D.	Clinical Director	Medical Affairs
	R.B. Rothman, M.D., Ph.D	Chief	Clinical Pharmacology Branch
	J.E. Henningfield, Ph.D.	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Neuropsychiatry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
5	4	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The purpose of this project is to continue to assess the neurological status of individuals who have abused cocaine and other drugs over a long period of their lives. The acute neuropsychiatric disorders include seizure, psychosis, subarachnoid hemorrhage, and thromboembolic phenomena. However, there are few studies which used the detailed classical neurological examination in order to classify possible different neurological syndromes that might be associated with the use of drugs of abuse. We have thus started to carry out thorough neurological and neuropsychological examination in subjects who are chronic cocaine or polydrug abusers and who are seronegative for HIV.

The results of these examinations continue to show evidence of nystagmus, abnormal eye pursuit, abnormal saccades, decreased reflexes, and increased jaw jerk. Vibration and position senses were also abnormal. The presence of nystagmus and increased jaw jerk in these subjects may be related to cocaine effects on brainstem pathways. The reflex and sensory abnormalities appear to correspond to a bilateral symmetric neuropathy. These results suggest that cocaine may cause deleterious effects on the nervous system by causing constriction of the vasa nervorum which supply the peripheral nervous system. These findings suggest a new line of investigation which will focus on the peripheral effects of this well known vasoconstrictor.

Cadet, J.L., Gendron, T., Lange, W.R., Henningfield, J.E., and Rothman, R.B. The Clinical Neurological Examination in Chronic Cocaine Abusers: Preliminary Findings. NIDA Monograph Series 141: 31, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00228-02 MNP

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Drug-induced Toxicity and Free Radicals

PRINCIPAL INVESTIGATOR

P.I.	Jean Lud Cadet, M.D.	Chief	Neuroscience Branch
	Pelin Sheng, Ph.D.	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Neuropsychiatry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project assesses the role that free radicals might play in the neurotoxic effects associated with amphetamine analogs. Towards that end, we determined the effects of drug of abuse on the dopamine and serotonin systems in adult transgenic mice which overexpress the scavenging enzyme, superoxide dismutase.

Oxygen-based radicals are toxic compounds that have been implicated in the causation of a number of neurotoxic and neuropathological events. It was suggested that the deleterious effects of drugs of abuse, including the by-products of their synthesis, might be related to the production of oxygen-based and of other reactive compounds. Several enzymes including catalase, glutathione peroxidase, and superoxide dismutase, protect the cells form oxidative stress.

Administration of methamphetamine (METH) also causes significant depletion in a number of mammalian species. The effects of METH were also tested in the SOD-Tg mice. In Non-Tg mice, acute METH administration caused significant decreases in DA and dihydroxyphenyl acetic acid (DOPAC) in the striata and cortices. In contrast, there were no significant changes in striatal or cortical DA in the SOD-Tg mice. Chronic administration of METH caused depletion of DA and DOPAC in only the striata of Non-Tg mice. We also tested the lethal effects of MDA and MDMA in these mice and found that the transgenic mice were also protected. These results suggest that amphetamine-induced neurotoxic and lethal effects might involve overwhelming oxidative stress to the organisms.

Cadet, J.L., Sheng P., Ali S., Rothman R., Carlson E., and Epstein C. Attenuation of methamphetamine-induced neurotoxicity in copper/zinc superoxide dismutase transgenic mice. J. Neurochem. 62: 380-383, 1994.

Cadet J.L., Ladenheim B., Baum I., Carlson E., and Epstein C. CuZn-superoxide dismutase (CuZnSOD) transgenic mice show resistance to the lethal effects of methylendioxyamphetamine (MDA) and of methylenedioxymethamphetamine (MDMA). Brain Res. (1994) in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00229-02 MNP

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Effects of Subdivision 6-OHDSA Injections on Cocaine Induced Behaviors

PRINCIPAL INVESTIGATOR

P.I.	Jean Lud Cadet, M.D.	Chief	Neuroscience Branch
	R.B. Rothman, M.D., Ph.D	Chief	Clinical Pharmacology Branch
	J.S. Partilla	Lab Manager	Clinical Pharmacology Branch
	P. Sheng, Ph.D.	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Neuropsychiatry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
5	3	2

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

These studies continue to assess the distribution of [125I]RTI-55-labeled dopamine and serotonin uptake sites in the rat brain. Cocaine exerts its addictive properties through the blockade of DA uptake sites. Studies have been done to characterize the specific effects of cocaine on the brain, using ligands which bind at more than the DA uptake sites. Effort is being made to develop ligand that are more specific to DA uptake sites. One of these ligands is [125I]RTI-55. We have determined the specific distribution of these sites in the rat central nervous system in a number of studies. In addition, we evaluated the effects of 6-OHDA lesions in the nigrostriatal DA pathway. Unilateral lesions of the nigrostriatal dopaminergic pathway were performed by the stereotaxic application of 6-OHDA in the caudate-putamen. 6-OHDA caused marked decreases in total [125I]RTI binding sites in the NAc and the CPu. Further analyses indicated that these decreases corresponded to changes in both 5-HT and DA uptake sites. These studies also helped to demonstrate that [125I]RTI-55 bind to 5-HT sites in the caudate-putamen and in the frontal cortex of rats. These experiments stress the important of both biochemical and lesion studies in order to characterize the anatomical distribution of monoaminergic uptake sites in the rat brain.

Cadet, J.L., Ordinez, S., C.M. Dersch, Brockington, A., Becketts. K.M., Partilla. J.S., de Costa. B.R., Rice. K.C., Carroll, F.I., Akunne, H.C., and Rothman, R.B. Quantitative Autoradiographic Evaluation of the Effect of 6-OH-Dopamine Lesions on Binding Site Labeled with the Cocaine Analog, [125I] RTI-55. NIDA Monograph Series 141: 252, 1994.

Akkunne H.C., Dersch C.M., Cadet J.L. Char G.U., Partilla J.S., de Costa B.R., Rice K.C., Carroll F.I., and Rothman R.B. Studies of the biogenic amine transporters. III. Demonstration of two binding sites for GBR12935 and [3H]BTCP in rat caudate membranes. J. Pharmacol. Exp. Ther. 268: 1462-1475, 1994

Rothman R.B., Cadet J.L., Akunne H.C., Silverthorn M.L., Baumann M., Partilla J.S., de Costa B.R., Rice K.C., Carroll F.I., Partilla J.S., Wang J.B., Uhl G., Glowa J. and Dersch C.M. Studies of the biogenic amine transporters. IV. Demonstration of a multiplicity of binding sites in rat caudate for the cocaine analog [125I]RTI-55. JPET (in press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00231092 CTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Evaluation of pharmacologic treatments of opioid and cocaine dependence

PRINCIPAL INVESTIGATOR

P.I.	Kenzie L. Preston, Ph.D.	Chief	Treatment Branch
	Ivan Montoya, M.D.	Visiting Fellow	Treatment Branch
	David Gorelick, M.D., Ph.	Chief	Treatment Branch
	Annie Umbrich, M.D.	Staff Fellow	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1.6	0.4

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project assesses the safety and efficacy of pharmacological treatments of cocaine and opioid abuse/dependence in clinical trials. Evidence from preclinical studies suggests that the reinforcing effects of cocaine are related to its inhibition of dopamine reuptake. Much of the work to develop pharmacological treatments of cocaine dependence has thus far focused on dopaminergic agents, though no dopaminergic agents have yet been shown to be effective in reducing cocaine use. An open trial testing the safety and efficacy of combination treatment with buproprion and bromocriptine, agents with dopaminergic activity, is underway and has so far shown a low incidence of side effects among treated subjects. This study is the first to apply the strategy of combining pharmacologic agents to increase the efficacy of individual agents in the treatment of cocaine dependence. Data collected to date suggest that the combination of bupropion and bromocriptine is safe and possibly effective for treatment of cocaine dependence.

The partial opiate agonist buprenorphine is a safe and effective treatment for opiate dependence. Some preclinical studies and uncontrolled clinical case series have suggested that buprenorphine might also be effective in reducing cocaine use by opiate addicts. A double-blind, controlled clinical trial is underway that directly evaluates the efficacy of buprenorphine in reducing both opiate and cocaine use in dually opiate- and cocaine-dependent patients.

Medically supervised withdrawal from opioids is a commonly used treatment but is usually not effective in establishing long-term abstinence because patients frequently relapse soon after completion of the withdrawal. A procedure for initiating naltrexone maintenance during withdrawal treatment is being developed to provide a more effective post-withdrawal treatment that includes pharmacological treatment with opioid antagonists. The efficacy of buprenorphine/naltrexone combinations is being tested in a clinical trial. The first phase of the study has been completed. The results suggest that administration of naltrexone on day 2 may increases opiate withdrawal at the beginning of treatment but leads to decreased withdrawal thereafter, compared to treatment with naltrexone placebo. This result may bear on the hypothesis that antagonists may produce partial resetting of the opiate receptor, resulting in a shorter duration of withdrawal. These data also support the development of cost-effective short-term inpatient opiate detoxification and early transition to opiate-free treatment using naltrexone.

Preston, K. L., Sullivan, J. T., Berger, P., and Bigelow, G. E. Effects of cocaine alone and in combination with mazindol in human cocaine abusers. Journal of Pharmacology and Experimental Therapeutics 1993; 267:296-307.

Strain, E. C., Preston, K. L., Liebson, I. A., and Bigelow, G. E. Precipitated withdrawal by pentazocine in methadone-maintained volunteers. Journal of Pharmacology and Experimental Therapeutics 1993; 267:624-634.

Strain, E. C., Preston, K. L., Stitzer, M. L., Liebson, I. A., and Bigelow, G. E. The effects of cocaine in buprenorphine-maintained outpatient volunteers: Results from clinical experience and laboratory challenges. The American Journal of Addictions 1994; 3:129-143.

Walsh, S. L., Preston, K. L., Stitzer, M. L., Cone, E.J ., and Bigelow, G. E. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. Clinical Pharmacology and Therapeutics 1994; 55:569-580.

Preston, K. L., J. T. Sullivan, Testa, M., and D. R. Jasinski. Psychopharmacology of transnasal butorphanol. Drug and Alcohol Dependence 1994; 35:159-167.

Walsh, S. L., Gilson, S. F., Jasinski, D. R., Stapleton, J. M., Phillips, R. L., Dannals, R. F., Schmidt, J., Preston, K. L., Grayson, R., Bigelow, G. E., Sullivan J. T., Contoreggi, C., and London, E. D. Buprenorphine reduces cerebral glucose metabolism in polydrug abusers. Neuropsychopharmacology 1994; 10:157-170.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 002320-02 CTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Evaluation of non-pharmacological treatments of substance abuse

PRINCIPAL INVESTIGATOR

P.I.	Kenzie L. Preston, Ph.D.	Chief	Treatment Branch
	Lino Covi, M.D.	Visiting Scientists	Treatment Branch
	Annie Umbricht, M.D.	Staff Fellow	Treatment Branch
	Ivan Montoya, M.D.	Visiting Fellow	Treatment Branch
	Charles R. Schuster, Ph.D.	Senior Scientist	Office of the Director

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2.1	1.7	0.4

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The section has continued to investigate two major non-pharmacological treatments of substance abuse. Last year a project was completed showing that a behavioral intervention, contingency management, was effective in decreasing cocaine use among a group of methadone maintenance patients. Patients in the contingency management group achieved substantially longer periods of sustained abstinence from cocaine use than persons in a yoked control group. A follow-up study is underway to refine the reinforcement protocol to improve rates of initiation and maintenance of abstinence. The original reinforcement schedule was designed to escalate in value so that the incentive grew as the length of time that patients were abstinent grew. Thus, there was a strong incentive to remain abstinent. The initial value of the vouchers, however, was small, and a number of subjects never achieved initial abstinence. In the current study, a bonus was added for the first few cocaine-negative urines and then faded out in order increase the proportion of subjects achieving abstinence; the escalating incentive value was retained to maintain abstinence.

The contingency management procedure is also being applied in a second study to improve compliance with naltrexone treatment. Clinical experience has shown that compliance with naltrexone treatment tends to be very poor, seriously compromising its clinical utility. The purpose of the study is to test the efficacy of contingency management for improving patient compliance with naltrexone treatment.

Counseling is an important element of virtually all drug abuse treatment; thus standardization and evaluation of counseling procedures is needed to establish effective treatment, whether counseling is the sole treatment or is given in combination with pharmacotherapy. A 12-week study was completed in which the efficacy of a standardized individual Cognitive/Behavioral/Interpersonal counseling program administered according to a specified therapy manual, given either twice weekly, once weekly, or every two weeks, were compared. Outcome measures included cocaine and other drug use (by self-report and urine toxicology), cocaine craving, psychological state, and psychosocial functioning. Preliminary analysis indicated that there were fewer initial drop-outs in the twice a week treatment group, but no significant differences in drug use outcome measures between groups after twelve weeks of treatment. The manual is currently being adapted for use in a group treatment format.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00233-02 CTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Development of Methods For Screening Pharmacologic Treatments of Substance Abuse

PRINCIPAL INVESTIGATOR

P.I.	Kenzie L. Preston, Ph.D.	Chief	Treatment Branch
	Ivan Montoya, M.D.	Visiting Fellow	Treatment Branch
	David Gorelick, M.D., Ph.	Chief	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.85	0.65	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

We have begun a program of research to develop a laboratory model of cocaine abuse using very low doses of oral cocaine, doses that produce measurable behavioral effects but minimal cardiovascular effects. The first protocol in this research program uses a drug discrimination procedure to explore the limits of human behavioral sensitivity to oral cocaine. Initially, subjects in this protocol are taught to distinguish 50 mg of oral cocaine from placebo using a drug discrimination procedure. Then subjects are exposed to 4 doses of oral cocaine (6.25 mg, 12.5 mg, 25 mg, and 50 mg) and placebo in random order across days to determine the lowest doses of cocaine that subjects can detect. Throughout all of these administrations the cardiovascular and self-reported mood effects of these cocaine doses are determined. The protocol is currently ongoing. Further studies are planned to study cocaine and opioid drug discrimination, cocaine and opioid self-administration studies, the pharmacodynamic and pharmacokinetic effects of coca tea, and a multiple-choice behavioral paradigm for screen medications.

Mumford, G. K., Evans, S. M., Kaminski, B. J., Preston, K. L., Sannerud, C. A., Silverman, K., and Griffiths, R. R. Discriminative stimulus and subjective effects of theobromine and caffeine in humans. Psychopharmacology 1994; 115:1-8.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00234-02 CTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Psychological and methodological issues in substance abuse treatment/research

PRINCIPAL INVESTIGATOR

P.I.	Kenzie L. Preston, Ph.D.	Chief	Treatment Branch
	Ivan Montoya, M.D.	Visiting Fellow	Treatment Branch
	Lino Covi, M.D.	Visiting Scientist	Etiology Branch
	David Gorelick, M.D., Ph.	Chief	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.4	0.1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The psychological assessment of subjects participating in clinical trials has become an important part of the section's research interest. Several studies were conducted: a comparison of drug abusers seeking treatment and not seeking treatment; an evaluation of personality disorders in cocaine dependent individuals seeking research treatment; and a survey of motivation for treatment.

An important issue facing researchers and treatment providers is the reporting and representation of women and minorities in cocaine abuse pharmacotherapy clinical trials. Sociodemographic representation in 61 reports of outpatient pharmacotherapy for cocaine abuse, published in refereed, English language journals, between 1983 and 1993 was compared to the epidemiology of frequent cocaine use in the 1990 NIDA National Household Survey of Drug Abuse (NIDA-HS). The findings showed that important sociodemographic data is often not reported in papers, and raise issues of quality of research reports, generalizability of results, social equity, and accessibility for certain groups in cocaine abuse pharmacotherapy research.

In procedural studies to identify improved outcome variable in clinical trials, the usefulness of quantitative urinalysis for cocaine metabolite and creatinine correction techniques and the relationship between these data and self-reported drug use were assessed with data collected in a clinical trial (N = 37) of a contingency management behavioral treatment intervention. Rules were developed to differentiate between occasions of new use and carry-over in positive qualitative urine tests. Preliminary analyses suggest: qualitative and quantitative urine testing show greater rates of drug use than that shown by self report; quantitative testing provides a means of differentiating incidences of new drug use from residual carry-over; the identification of new use with quantitative testing may help to reconcile differences between rates of drug use indicated by qualitative urine screens and self-report.

Sweat patches have been proven effective in measuring cocaine and opiate use in controlled clinical laboratory settings but have not previously been tested under more realistic settings such as our treatment clinic. Collection of sweat as a method of monitoring drug use may be more accurate and reliable over a longer period of time than the urine testing method currently used. The purpose to evaluate the effectiveness of collecting sweat as an alternative method of monitoring drug use. Results will be compared to drug use as monitored by urine samples collected three times a week.

Montoya, I.D.; Hess, J.M.; Covi, L.; Fudala, P.J.; Johnson, R.E.: A Comparative Study of Psychopathology and Cognitive Functions between Cocaine and Opiate Dependent Patients Seeking Treatment. American Journal of Addictions 1994; 3:36-42.

Montoya, I.D.; Haertzen, C.A.: Reduction of Psychopathology Among Individuals Participating in Non-treatment Drug Abuse Residential Studies. Journal of Addictive Diseases 1994; 13: 89-97.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00235-02 CDM

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Detection of Drugs of Abuse in Human Sweat

PRINCIPAL INVESTIGATOR

P.I.	E.J. Cone	Chief	Clinical Pharmacology Branch
	W.D. Darwin	Chemist	Clinical Pharmacology Branch
	A. Jenkins	IRTA	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Sweat was evaluated as a media for use in monitoring drug use by human subjects. Healthy subjects with a history of chemical substance abuse volunteered for these studies. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Following the administration of cocaine, marijuana or opiates, sweat samples were collected periodically. Other biological specimens like saliva, blood, urine and hair also were collected. Specimens were analyzed by immunoassay and gas chromatography/mass spectrometry.

These data will provide new information on this unusual biological specimen which may be useful in development of methods for monitoring human drug exposure.

Cone, E.J., Hillsgrove, M.J., Jenkins, A.J., Keenan, R.M. and Darwin, W.D. Sweat Testing For Heroin, Cocaine And Metabolites. J. Anal. Toxicol. in press, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00236-02 MPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Opioids and Organ Preservation

PRINCIPAL INVESTIGATOR

P.I. T.P.Su, Ph.D. Research Chemist Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The organ preservation effect of opioids is examined in a single organ preservation preparation. Rat lungs are dissected and preserved in hypothermic solutions with or without a delta opioid peptide DADLE. DADLE markedly enhances the hypothermic preservation time of isolated rat lungs. The functions of the hypothermically preserved lungs with added DADLE are comparable to the functions of the controls which are dissected and studied immediately. Lungs preserved without DADLE functioned poorly in the test.

Chien S, PR Oeltgen, JN Diana, RK Alley and T-P Su (1994): Extension of tissue survival time in multiorgan block preparation using a delta opioid DADLE. J. Thorac. Cardiovasc. Surg., 107:964-967.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00237-02 NDAS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Ligand Development and Imaging Studies of Sigma (s) Receptors

PRINCIPAL INVESTIGATOR

P.I. E.D. London Chief Neuroscience Branch

COOPERATING UNITS

Johns Hopkins Medical School
University of Kentucky

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project aims to develop radioligands for s receptors, and to elucidate functions of these receptors, which have been implicated in a various biological processes. [H-3]-ifenprodil binding demonstrated saturability and high-affinity. Competition assays and studies of and neuroanatomical and subcellular distribution indicated that at 4° C the radioligand labeled polyamine binding sites on the N-methyl-D-aspartate (NMDA) receptor but that at 37° C, it bound s receptors. The pharmacological profile of [H-3]ifenprodil binding was highly correlated with that of s-2, but not s-1 sites. Because [H-3]ifenprodil labels s-2 sites, isomers and analogues of ifenprodil were compared as potential s-2 ligands. Of the compounds tested, threo- and erythro-ifenprodil had the highest affinity for s-2 sites. Threo-ifenprodil, which has less affinity for a1-adrenergic receptors than erythro-ifenprodil, was more selective than erythro-ifenprodil for s-2 sites. These results identify threo-ifenprodil as more useful for studies of s-2 receptors than other compounds.

4-Phenyl-1-(4-phenylbutyl)piperidine (4-PPBP) had been identified as a s ligand with high affinity. Studies of [H-3]4-PPBP demonstrated that it is one of the highest affinity s ligands described to date, and that it is potentially useful as radioligand for in vivo labeling of cerebral s receptors.

Because previous data suggested that drugs which interact with s receptors may afford neuroprotection in cases of transient ischemia, we assessed whether 4-PPBP would decrease brain injury from transient middle cerebral artery occlusion (MCAO). Halothane-anesthetized, cats underwent unilateral MCAO and by reperfusion. Cats given 1mmole/kg/h 4-PPBP (from 74 min of MCAO to 4 h reperfusion) had a smaller injury volume in the ipsilateral hemisphere, inferior temporal cortex, and lateral temporal-parietal cortex than cats given saline or low 0.1 mmole/kg/h 4-PPBP. The results suggest that s receptors may mediate neuroprotection in a model of temporary focal ischemia.

Aminoalkylpyridines (AAPs) have high selectivity for s-1 sites in rat brain and show high correlation between s-1 affinity and anticonvulsant potency. The results suggest that the anticonvulsant activity of AAPs may be due to selective, low affinity interactions at s-1 receptors.

Hashimoto K, Mantione CR, Spada MR, Neumeyer JL, London ED. Further characterization of [H-3]ifenprodil binding in rat brain. Eur J Pharmacol 1993;266:67-77.

Hashimoto K, London ED. Imaging Sigma receptors and cerebral responses to Sigma drugs. In: Itzhak Y, ed. The Sigma Receptors. Miami: Academic Press, 1994;225-242.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00238-02 NDAS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

BIOASSAY, A Statistical Analysis Program

PRINCIPAL INVESTIGATOR

P.I. D.B. Vaupel Pharmacologist Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The parallel line bioassay is a classical statistical technique used in pharmacology to estimate the relative potency of a test compound relative to a standard drug. Unfortunately, this complex analysis is not available on commercial statistical analysis software. Therefore, shortcut methods, that are not based on a valid statistical process are used to obtain relative potency estimates. A user-friendly statistical analysis program, entitled BIOASSAY, using the parallel line bioassay being as core procedure, is being developed and written in C++ for use with DOS systems. The program is designed to make more efficient use of balanced experimental designs, such as those used for human and primate pharmacological studies, but it may be used with in vitro studies as well. Also included are other statistical tests which are useful in analyzing dose-response data: linear regression, Dunnett's test, missing values calculations, Scheffe-Box test for homogeneity of variance, t-tests and a data transformation routine. Data may be imported from LOTUS files, and there are three ways to output the final analyses. The unique statistical advantages of the program include: the calculation of relative potency estimates and confidence limits based on linear, parallel portions of two dose-response curves for equi-effective drug effects; partitioning out a Between Subjects variance component with the parallel line, linear regression and Dunnett's tests; calculating missing values for randomized block experimental designs and making the appropriate corrections in the ANOVA; and having the capability of making inverse predictions with confidence limits from linear dose-response curves (i.e. estimating the dose of a drug required to produce a given effect). The scope of the project encompasses program development, validation studies and preparation of an instruction manual. At this time, programming is complete, validation is in progress, and a draft of the instruction manual has been prepared.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00239-02 BPGS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Peripheral Mechanisms of Opioid Analgesia

PRINCIPAL INVESTIGATOR

P.I.	Steven Goldberg, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Christoph Stein, M.D.	Guest Scientist	Preclinical Pharmacology Laboratory
	Michael Schaefer, M.D.	Visiting Fellow	Preclinical Pharmacology Laboratory
	Shaaban Mousa, Ph.D.	Guest Scientist	Preclinical Pharmacology Laboratory

COOPERATING UNITS

Johns Hopkins School of Medicine

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
4.1	3.1	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

With regard to their analgesic effects, opioids have been thought to act on receptors within the central nervous system exclusively. Recently, however, we have shown that, within inflamed rat paws, immune-cell derived opioid peptides can activate peripheral opioid receptors located on sensory nerves and induce antinociception. The purpose of our current research is to examine agents for their capability of releasing opioid peptides from immune cells and for their potential in the inhibition of pain. Such peripheral effects are of considerable interest in view of the avoidance of centrally mediated side effects of opioid analgesics, such as dysphoria, dependence, addiction, sedation and respiratory depression. Our most recent experiments have examined whether corticotropin releasing factor (CRF) or interleukin-1Beta (IL-1Beta) release opioid peptides in inflamed tissue and result in analgesia. Upon administration of CRF or IL-1Beta into both paws of rats with unilateral hindpaw inflammation, nociceptive thresholds increase markedly in the inflamed but not in the noninflamed paw. Alpha-helical-CRF and interleukin-1 receptor antagonist, respectively, antagonize this analgesic effect, indicating that CRF and IL-1Beta act via their specific receptors. These receptors are most likely localized on immune cells within the inflamed tissue because immunosuppression by cyclosporin A attenuates the effect. In experiments with antisera against opioid peptides we have shown that endogenous opioids released from immune cells mediate these analgesic effects. This is supported by the fact that naloxone and other opioid antagonists reverse these effects. These results suggest that CRF and IL-1Beta, by activation of their receptors on immune cells, cause a release of opioids which subsequently occupy their receptors on sensory nerves resulting in inhibition of pain. Ongoing in vitro experiments examine whether CRF or IL-1Beta are capable of releasing endorphin in cell suspensions prepared from inflamed and noninflamed lymph nodes and whether this release can be attenuated by the respective antagonists. To further elucidate the mechanisms governing the apparent "upregulation" of opioid receptors on sensory nerves during inflammation, we are examining the permeability of the perineurial barrier by histochemistry and the expression of opioid receptor genes in dorsal root ganglia.

Schaefer M, Carter L, Stein C. Interleukin-1ß and corticotropin releasing factor inhibit pain by releasing opioids from immune cells in inflamed tissue. Proc Natl Acad Sci USA 1994;91:4219-23.

Antonijevic I, Mousa SA, Schaefer M, Stein C. Perineurial defect and peripheral opioid analgesia in inflammation, J Neuroscience 1994; in press.

Stein C, Schaefer M, Carter L, Czlonkowski A, Mousa S, Epplen C. Cytokine-induced antinociception mediated by opioids released from immune cells, Regulatory Peptides 1994;50:S191-2.

Mousa SA, Mitchell WM, Hassan AHS, Carter L, Stein C. Corticotropin releasing factor receptors in inflamed tissue: autoradiographic identification, Regulatory Peptides 1994; in press.

Schaefer M, Carter L, Stein C. Interleukin-1- and corticotropin releasing factor-induced release of ß-endorphin from immune cells and inhibition of inflammatory pain, Regulatory Peptides 1994: in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00240-02 PTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Development of New Pharmacologic and Biologic Treatments for Drug Dependence

PRINCIPAL INVESTIGATOR

P.I.	David. A. Gorelick, M.D.,	Chief	Treatment Branch
	Lawrence Cheskin, M.D,	Senior Staff Fellow	Treatment Branch
	Richar Nelson, M.D.	Clinical Associate	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.9	1.5	0.4

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project assesses the efficacy and safety of new pharmacologic and biologic treatments for drug dependence using experimental paradigms in a controlled, residential environment. Some animal and open-label human studies suggest that the anti-convulsant carbamazepine may reduce cocaine craving and use, possibly by blocking the development of cocaine-induced kindling. However, a recently completed double-blind study did not support the efficacy of carbamazepine in the treatment of cocaine dependence.

In humans, very low calorie diets producing ketonemia are associated with the absence of hunger, but it is not known whether this subjective effect also applies to drugs of abuse. In animals, balanced low calorie diets not producing ketonemia increase drug self-administration. A second component of this project is evaluating which of these dietary effects operates in human drug abusers, using nicotine (cigarette smoking) as the target drug. Preliminary results indicate that a balanced low calorie diet increases cigarette smoking, while a low calorie ketogenic diet does not alter smoking. These findings have clinical implications, especially since some drugs of abuse themselves suppress appetite and thus may produce calorie deprivation.

The primary enzyme metabolizing cocaine in humans is butyrylcholinesterase. In theory, alterations in enzyme activity might alter brain levels of cocaine and its metabolites and thus alter cocaine's effects, with possible therapeutic benefits. In a collaborative study with the Preclinical Pharmacology Laboratory and the National Institute on Aging, compounds which alter butyrylcholinesterase activity are given to monkeys to determine whether they alter the acute effects of cocaine.

PUBLICATIONS

Crowell MD, Cheskin LJ, Musial F. Prevalence of gastrointestinal symptoms in obese and normal weight binge eaters. American Journal of Gastroenterol, 89(3):387-391, 1994.

Lamport RD, Cheskin LJ, Moscatellos SA, Nikoomanesh P. Sterile epidural and bilateral psoas absesses in a patient with Crohn's disease. American Journal of Gastroenterol, 89(7):1086-1089, 1994.

Cheskin LJ. Gastrointestinal bleeding. In: Barker LR, Burton J, Zieve PD (eds). Principles of Ambulatory Medicine, 4th ed. Williams and Wilkens, Baltimore, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00241-02 PTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Identification of factors associated with response to drugs and treatment

PRINCIPAL INVESTIGATOR

P.I. David A. Gorelick, M.D., P Chief Treatment Branch

Richard Nelson, M.D., Clinical Associate Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.6	0.9	0.3

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Drug abusers vary widely in their acute and chronic responses to drugs and in their compliance with and response to drug abuse treatment. A better understanding of the factors associated with individual differences in response should result in the development of more effective and efficient treatment interventions. This project assesses several biological and psychosocial characteristics of drug abusers and correlates them with abusers' response to their abused drug or to the abusers' treatment compliance and outcome.

One component, in collaboration with Dr. Raymond Woosley, Department of Pharmacology, Georgetown University, measures activity of the plasma enzyme butyrylcholinesterase, the main cocaine-metabolizing enzyme in humans. Preliminary results indicate that cocaine addicts tend to have normal enzyme activity, which can vary four-fold between addicts. A second component assesses psychiatric co-morbidity, personality traits, mood, neuropsychological function, and sociodemographic characteristics in drug abusers using structured and semi-structured diagnostic interviews and computer-administered psychological tests. A third component, in collaboration with Dr. James Frost, Department of Radiology, Johns Hopkins University, uses positron emission tomography (PET) scanning to evaluate the effect of chronic cocaine abuse on mu-opiate receptor function in the brain, and the relationship between such receptor function and the severity and time course of cocaine withdrawal. Another component, in collaboration with the Molecular Neurobiology Laboratory, assesses various neurotransmitter-associated genotypes with the goal of identifying alleles significantly associated with particular substance use disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00242-02 PTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Prevention or amelioration of biomedical consequences of drug abuse

PRINCIPAL INVESTIGATOR

P.I. David A. Gorelick, M.D., P Chief Treatment Branch

Richard A. Nelson, M.D. Clinical Associate Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Drug abuse has serious, often lethal, biomedical consequences, such as HIV infection and cardiovascular dysfunction. This project studies subject characteristics, high-risk behaviors, and other factors associated with such consequences, with the goal of developing interventions to prevent or ameliorate them. One study currently underway provides a comprehensive, non-invasive assessment of cardiovascular function in cocaine abusers, using 24-hour ambulatory monitoring of EKG, blood pressure, and heart rate; high-resolution EKG; analysis of heart rate variability (vagal tone), and echocardiography. Evaluation of the subclinical effects of acute and chronic cocaine use on cardiovascular function will help elucidate the mechanisms of cocaine's cardiovascular effects, hopefully leading to their prevention or amelioration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00243-02 PTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Development of Human Experimental Methods for Evaluating Drug Abuse Thearpy

PRINCIPAL INVESTIGATOR

P.I. David A. Gorelick, M.D., P Chief Treatment Branch

Richard Nelson, M.D. Clinical Associate Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.1	0.3

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Most existing methods for evaluating the efficacy and safety of pharmacotherapies for drug abuse involve either the time and expense of clinical treatment trials or short-term experimental models which have the medical risk of drug administration and whose relevance to clinical drug abuse may be questionable. The goal of this project is to develop human experimental methods in a controlled residential research ward environment which can safely and efficiently be used to evaluate potential treatment medications. One study has used a drug self-administration paradigm analogous to those used in animal research, in which human subjects could make a stimulus-controlled operant response to earn an iv injection of low-dose cocaine or saline. Results showed that cocaine abusers could distinguish cocaine from saline injections and found the former highly reinforcing and the latter non-reinforcing. Data from the study are being analyzed to evaluate the relationship between drug self-administration and craving for cocaine, since the latter is often used as a surrogate outcome variable in studies of drug abuse treatment. Two different methods for measuring cocaine craving, visual-analogue scales and Likert scales, are also being evaluated.

Another component is studying conditioned or context-specific behavioral sensitization as a method for evaluating clinically relevant effects of cocaine. While this phenomenon has been demonstrated in animals. it has never been demonstrated in humans.

Kato K, Hillsgrove M, Weinnold L, Gorelick DA, Darwin WD, & Cone EJ: Cocaine and metabolite excretion in saliva under stimulated and nonstiumlated conditions. Journal of Analytical Toxicology, 17:338-341, 1993.

Stein RA, Jarvik ME, & Gorelick DA. Impairment of memory by fluoxetine in smokers. Experimental and Clinical Psychopharmacology 1:188-193, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00244-02 PTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Evaluation of existing treatments for drug abuse

PRINCIPAL INVESTIGATOR

P.I. Sharyn Greberman, Sc.D. IRTA — Treatment Branch

David A. Gorelick, M.D., P Chief — Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Pharmacotherapy

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.05	1.05	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project is evaluating factors associated with drug users seeking treatment in a hospital emergency room. Drug users may present to a hospital emergency room for a variety of reasons, some clinically appropriate (e.g., a life-threatening medical consequence of drug use) and some less efficient uses of the health care system (e.g., non-urgent medical condition, attempt to enter substance abuse treatment). There is little data available on the relationship between emergency room visits by drug users and their seeking of and participation in drug abuse treatment. This study, in collaboration with the Department of Emergency Medicine at the Hopkins Bayview Medical Center, Baltimore, MD, collects data on the sociodemographic, drug use, and treatment-seeking behavior of an unselected series of drug users visiting an urban hospital emergency room.

Another component in collaboration with the Clinical Dependency Unit at the Hopkins Bayview Medical Center, is evaluating the influence of medical ? morbidity and prior medical and substance abuse treatment on the response to short-term inpatient detoxification treatment for substance abuse.

Ball, J.C. "Why Has It Proved So Difficult to Match Drug Abuse Patients To Appropnate Treatment?" Addiction, 89(3):263-266, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00246-02 BDS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Determinants of Drug Abuse Liability

PRINCIPAL INVESTIGATOR

P.I.	Stephen Heishman	Research Psychologist	Clinical Pharmacology Branch
	Jack Henningfield	Chief	Clinical Pharmacology Branch
	Charles Schuster	Senior Scientist	Office of the Director
	Leslie Schuh	IRTA	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	2	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Psychoactive substances vary considerably in their abuse liability. For example, major tranquilizers typically do not maintain self-administration , whereas smokable forms of nicotine and cocaine are highly addictive. Quantification of the differences among drugs in terms of abuse liability and discovering the mechanisms that underlie these differences is fundamental in the development of safer medications in general and in developing more effective medications for the treatment of addictive disorders. Two strategies for human evaluation of the mechanisms of drug abuse liability are drug discrimination and drug self-administration. Both of these paradigms evolved from animal research, and their application to humans makes it possible to apply animal and human data to identify mechanisms of addiction.

Currently, we are using the drug discrimination paradigm to explore the mechanisms underlying the distinction between the high abuse liability profile of stimulants such as amphetamine and the lower abuse liability of other stimulants such as caffeine. A series of three studies investigates the subjective and discriminative effects of several stimulant drugs that are widely sold via mail order and designed to imitate amphetamine-like stimulants. These so called "look-alike" stimulants contain caffeine alone or combined with one or more sympathomimetic amines, such as ephedrine and phenylpropanolamine (PPA). Little is known about the behavioral pharmacology in humans of the combined effects of these drugs, including effects when individuals exceed the therapeutic dosage in an attempt to achieve amphetamine-like euphoria. These studies, which are in progress, are investigating the drugs singly and in combination.

Another series of studies in progress is attempting to refine the drug self-administration paradigm to allow more systematic evaluation of the reinforcing effects of opioids. The initial study of opioid self-administration will then be extended to evaluate the role of behavioral factors and medications in modulating the reinforcing effects of opioids.

Henningfield, J. E., & Heishman, S. J. (in press). The addictive role of nicotine in tobacco use. Psychopharmacology.

Henningfield, J. E., Schuh, L. M., & Heishman, S. J. (in press). Pharmacological determinants of cigarette smoking. In P. B. S. Clarke, M. Quik, F. X. Adlkofer, & K. Thurau (Eds.), Effects of nicotine on biological systems (pp. 000-000). Basel: Birkhauser Verlag.

Heishman, S. J., & Henningfield, J. E. (in press). Is caffeine a drug of dependence? Criteria and comparisons. Pharmacopsychoecologia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00247-02 BDS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Behavioral Mechanisms of Drug Effects

PRINCIPAL INVESTIGATOR

P.I.	Stephen Heishman	Research Psychologist	Clinical Pharmacology Branch
	Jack Henningfield	Chief	Clinical Pharmacology Branch
	Richard Taylor	Research Psychologist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	1	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The mechanisms by which drugs affect human behavior are complex, involving the interaction between the direct actions of the drug (e.g., impaired coordination) and the functional behavioral effects such as altered motivation. Specific determinants of drug response include the drug dose, the route of administration, the person's physiological and psychological state, the particular environmental conditions, and the nature of the behavior or test used. One approach we are pursuing is to vary the environmental conditions by mainpulating the reinforcement (monetary) contingencies under which subjects perform various tasks. This can be thought of as manipulating a subject's motivation to perform. By also varying drug dose and using tests that measure different aspects of performance (e.g., psychomotor vs. cognitive), we can begin to explore the complex interactions underlying the effects of drugs on behavior.

Another approach to investigating the mechanisms by which drugs influence behavior is to focus on performance impairment produced by psychoactive drugs. The performance-impairing effects of abused drugs produce a large toll on the nation each year in terms of traffic injuries and fatalities and lost productivity in the workplace. However, for most drugs, we lack basic knowledge about the behavioral mechanisms underlying their impairment of human performance. A series of studies is being conducted that will address such questions. A battery of physiological, behavioral, and performance measures designed to determine whether an individual is behaviorally impaired as the result of taking a drug has been tested with ethanol, marijuana, and cocaine. A study scheduled to begin in September, 1994 will examine the effects of amphetamine, codeine, and alprazolam on this same test battery as well as a cognitive test of attention and memory. By also collecting blood samples during these studies, we will be able to gain valuable information conceming the relationship between plasma concentrations of drugs and degree of performance impairment.

PUBLICATIONS

Heishman, S. J. (in press). Laboratory performance assessment: Impairing effects of psychoactive drugs. NIDA Research Monograph. Washington, DC: U.S. Govemment Printing Office.

Heishman, S. J., Taylor, R. C., & Henningfield, J. E. (in press). Nicotine and smoking: A review of effects on human performance. Experimental and Clinical Psychopharmacology.

Heishman, S. J. (in press). Strengths and weaknesses in the application of laboratory performance assessment to workplace settings. In H. S. Axel & D. J. Crouch (Eds.), Research Methods in Workplace Settings. NIDA Research Monograph. Washington, DC: U.S. Government Printing Office.

Fiore, M., Shi, F. Y., Heishman, S. J., Henningfield, J. E. The effect of smoking and smoking withdrawal on flight performance: A 1994 update. Report to Centers for Disease Control and Prevention.

Heishman, S.J., Snyder, F.R. and Henningfield. J.E. Performance, subjective, and physiological effects of nicotine in non-smokers. Drugs and Alcohol Dependence, 34: 11-18, 1993.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00248-02 BDS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Neurophysiologic, performance and subjective effects of nicotine.

PRINCIPAL INVESTIGATOR

P.I.	Wallace Pickworth	Research Pharmacologist	Clinical Pharmacology Branch
	Jack Henningfield	Chief	Clinical Pharmacology Branch
	Jean Lud Cadet	Chief	Neuroscience Branch
	Stephen Heishman	Research Psychologist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.65	0.6	0.05

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Several clinical studies are being performed to determine objective and subjective measures associated with smoking and tobacco withdrawal. The results of these studies are being applied to develop paradigms for testing drugs for the treatment of nicotine withdrawal. Neurophysiologic data indicate the mechanisms of nicotine's effects and its withdrawal on neural substrates involved in attention, cognition and memory. For example, the effects of mecamylamine, a centrally acting nicotinic antagonist, is studied to determine the contribution of tonic cholinergic mechanisms on the EEG and cognitive tasks in smokers and nonsmokers. The ability of transcranially delivered electrostimulation to alleviate nicotine withdrawal was evaluated in a treatment protocol. The efficacy of transdermally delivered nicotine to diminish signs and symptoms of spontaneous tobacco withdrawal are tested in a residential study. The effects of nicotine withdrawal on delayed auditory feedback, a proposed measure of attention and distraction, is being evaluated. The interaction of caffeine and nicotine after overnight abstinence was assessed. Dependent measures for these studies include Gordon vigilance task (with and without distracters), word memory, PAB (performance) spontaneous EEG, evoked potentials, blood pressure, heart rate (physiologic), withdrawal scales, craving, drug liking, drug identification (subjective). These studies are not only helping us to unravel the mechanisms of nicotine addiction but are also of practical value in the development of more effective medications for treating nicotine dependence and withdrawal.

PUBLICATIONS

Cohen, C., Pickworth, W.B., Bunker, E.B. and Henningfield, J.E. Caffeine antagonizes EEG effects of nicotine withdrawal. Pharmacology Brochemistry and Behavior 47: 919-926, 1994.

Cohen, C., Pickworth, W.B. and Henningfield, J.E. Pharmacologic characteristics of tobacco dependence. In: Prevention of Respiratory Disease, Hirsch et al (eds) 1993, pp. 545-558.

Henningfield, J.E., Cohen, C. and Pickworth, W.B. Psychopharmacology of nicotine. In: Nicotine Dependence. C. T. Orleans, J. Slade (eds) ,Oxford Press, 1993 pp. 24-45.

Pickworth, W.B., Keenan, R.M. and Henningfield, J.E. Nicotine: Effects and Melchanisms. In: Handbook of Neurotoxicology, Volume 2 Chang and Dyer, (eds) Marcel Dekker, New York, 1994 (in press).

Pickworth, W.B., Bunker, E.B. and Henningfield, J.E. Transdermal nicotine; reduction of smoking with minimal abuse liability. Psychopharmacology 115:; 9-14, 1994.

Butschky, M.F., Bailey, D., Henningfield, J.E. and Pickworth, W.B. Smoking without nicotine delivery decreases withdrawal in 12-hr abstinent smokers. Pharmacology Biochemistry and Behavior, 1994 (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00249-02 BDS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Addiction Research Center Inventory Multilingual Versions

PRINCIPAL INVESTIGATOR

P.I.	Edward Singlton	Senior Staff Fellow	Clinical Pharmacology Branch
	Jack Henningfield	Chief	Clinical Pharmacology Branch
	Mi Li	Guest Scientist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

The most widely used instrument to quantitate the psychological effects of drugs of abuse and characterize their addictive potential is the ARC Inventory, but little cross-cultural work has been attempted with the instrument. A Spanish version was developed by investigators in Barcelona, and a Chinese version was developed in collaboration with investigators in Beijing. Preliminary studies have been conducted with each, and the data are undergoing evaluation. The Spanish version is being evaluated to assess this translation's relevance to literate and Spanish speaking adults in the United States. The sample was composed of adults from Houston, Texas with a reported history of polysubstance abuse. Each had at least a seventh grade reading level and was literate in the Standard Spanish language as written in Texas. The Chinese version has been given an initial test in China by our collaborators. Data analysis from these studies is underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00306-08 CDM

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Pharmacokinetics and Pharmacodynamics of Opiate Analgesics

PRINCIPAL INVESTIGATOR

P.I.	E.J. Cone	Chief	Clinical Pharmacology Branch
	W.D. Darwin	Chemist	Clinical Pharmacology Branch
	D. Yousefnejad	Chemist	Clinical Pharmacology Branch
	A. Jenkins	IRTA	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The pharmacokinetic and pharmacodynamic effects of single doses of parenterally administered opiates (heroin, morphine, hydromorphone, codeine, oxycodone, oxymorphone and sublingual buprenorphine) were studied. Concentrations of drug in blood and saliva levels were compared to pharmacologic effects. Additionally, the study was performed to determine if a metabolic marker for heroin abuse could be found in urine and other biological fluids.

The subjects were healthy males with a history of heroin abuse. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. A total of three test doses (placebo and two active doses) were administered in random order. Test measures were made for 24 hours and biological fluids were collected for 7 days after each test. The biological fluids were analyzed for drug and metabolites by chromatographic and immunoassay techniques.

The significance of this study lies in the characterization of drug and metabolites appearance and disappearance over time in various bodily fluids and their relationship to drug-induced effects. Also, this continues our search for metabolite markers for heroin and other opiates in urine, saliva and other biological samples.

PUBLICATIONS

Goldberger, B.A., Darwin, W.D., Grant, T.M., Allen, A.C., Caplan, Y.H. and Cone, E.J. Measurement Of Heroin And Its Metabolites By Isotope-Dilution Electron-Impact Mass Spectrometry. Clin. Chem. 39: 670-675, 1993.

Cone, E.J., Holicky, B.A., Grant, T.M., Darwin, W.D. and Goldberger, B.A., Pharmacokinetics and Pharmacodynamics of Intranasal "Snorted" Heroin. J. Anal. Toxicol., 17: 327-337, 1993.

Walsh, S., Preston, K., Stitzer, M., Cone, E.J. and Bigelow, G., Clinical Pharmacology of Buprenorphine: Ceiling Effects at High Doses. Clin. Pharmacol. Ther., In Press, 1993.

Cone, E.J., Dickerson, S.L., Paul, B.D. and Mitchell, J.M., Forensic Drug Testing For Opiates V. Urine Testing For Heroin, Morphine And Codeine With Commercial Opiate Immunoassays. J. Anal. Toxicol., 17: 156-164, 1993.

Jenkins, A.J., Goldberger, B.A., Cone, E. J. and Hoey, D.E. GC/MS Assay of 6-Acetylmorphine in Plasma. Hewlett-Packard MS Application Note, MS 93-3.

Goldberger, B.A. and Cone, E.J. Confirmatory Tests For Drugs in the Workplace by gas chromatography-mass spectrometry. J. Chromatogr., In Press, 1994.

Smith, M.L., Hughes, R.O., Levine, B., Dickerson, S.L., Darwin, W.D. and Cone, E.J. Forensic Drug Testing For Opiates. VI. Urine Testing For Hydromorphone, Hydrocodone, Oxymorphone And Oxycodone With Commercial Opiate Immunoassays and Gas Chromatography/Mass Spectrometry. J. Anal. Toxicol., In Press, 1994.

Goldberger, B.A., Lowenthal, B., Darwin, W.D. and Cone, E.J. Intrasubject Variation Of Creatinine, Specific Gravity And pH Measurements In Consecutive Urine Specimens in Heroin Users. Clin. Chem, In Press, 1994.

Pickworth, W.B., Bunker, E., Welch, P. and Cone, E., Intravenous Buprenorphine Reduces Pupil Size And The Light Reflex In Humans, Life Sciences, 49: 129-138, 1990.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00310-06 CDM

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Assessment of the Risk of Passive Inhalation of Drugs of Abuse

PRINCIPAL INVESTIGATOR

P.I.	E.J. Cone	Chief	Clinical Pharmacology Branch
	W.D. Darwin	Chemist	Clinical Pharmacology Branch
	D. Yousefnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.6	0.1	0.5

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

When drugs of abuse are smoked, volatile components and pyrolysis material escape into the atmosphere. Depending on the local environment, bystanders may be exposed to the drug by passive inhalation of the contaminated air.

Artificial methods have been developed to smoke drugs of abuse in a controlled environment and to measure drug air levels. These methods are then applied to the design of human clinical studies to assess the hazards of environmental exposure to drugs. Six subjects were exposed to vaporized cocaine in a small unventilated room. The study was performed under blind conditions with placebo control and two active doses of cocaine. Urine, blood and saliva samples indicated that subjects were exposed to cocaine, but sufficient amounts were not absorbed to produce pharmacological effects or test positive at standard cutoff concentrations.

Unknowing drug exposure could be dangerous to unsuspecting bystanders, particularly to small children. These studies will establish limits of exposure to volatile components of drugs under controlled conditions.

PUBLICATIONS

Gleason, C.A., H. Iida, T. P. O'Brien, M. Douglas Jones Jr., E. J. Cone and R. J. Traystman. Fetal Responses To Acute Maternal Cocaine Injection In Sheep. Amer. J. Physiol., 34, H9-H14, 1993.

O'Brien, T.P. , Gleason, C.A., Jr., Jones, D., Cone, E.J., London, E.D. and Traystman, R.J. Cerebral Responses To Single And Multiple Cocaine Injections In Newborn Sheep. Pediatric Research, 35; 339-343, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00312-06 NDAS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Ligand-gated Ion Channels: N-Methyl-D-aspartate and Nicotinic Receptors

PRINCIPAL INVESTIGATOR

P.I.	E.D. London	Chief	Neuroscience Branch
	A. Mukhin	Visiting Scientist	Neuroscience Branch
	T. Matsunaga	Visiting Fellow	Neuroscience Branch
	J. Bell	Pharmacologist	Neuroscience Branch
	D.K. Ingram	Research Psychologist	Neuroscience Branch
	A. Shimada	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Neuroimaging and Drug Action

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.23	1.23	0

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

This project focuses on N-methyl-D-aspartate (NMDA) and nicotinic cholinergic receptors (NMDA-R, nAChR), ligand-gated ion channels. NMDA-R is involved in the psychotropic actions of phencyclidine, and in opioid tolerance and dependence; nAChR is the primary site of action of nicotine.

This research aims to clarify mechanisms by which polyamines (PAs) modulate function of NMDA-R and other neurotransmitter receptors or transporters. NMDA recognition sites in brain occur in two affinity states, and PAs (as well as mono- and divalent cations) convert these sites from the low- to the high-affinity conformation. PAs also enhance binding of [H-3]dizocilpine (DZ), even at saturating glutamate and glycine concentrations. Furthermore, arcaine, a PA antagonist, which inhibits the facilitation by PAs of DZ binding at saturating concentrations of glutamate, does not affect conversion between affinity states. Arcaine-sensitive modulation may involve enhancement in the efficiency of transduction between NMDA-R activation and channel opening, or it may involve an action of PAs to increase affinity of NMDA-R for DZ.

Studies of interactions of spermine (SP) with cocaine binding to dopamine and serotonin transporters (DAT, ST, respectively) showed that SP inhibited binding of [H-3]CFT and [H-3]mazindol to DAT, but had no effect on binding of [H-3]paroxetine to ST. The effect of SP on binding to DAT involved a decrease in the density of binding sites. The results suggest that PAs can alter effects of cocaine, and they have implications for treatment of cocaine abuse.

As an extension of our previously demonstration that ascorbic acid (AA) protects neurons in culture from NMDA toxicity, we examined potential neuroprotective effects of AA against toxicity produced by nitric oxide (NO), generated from the breakdown of sodium nitroprusside (SNP). Although AA protected against NMDA toxicity, it enhanced toxicity produced by SNP. The data support a model in which the redox state of NO determines whether the free radical produces neuroprotection or neurotoxicity.

[H-3]Cytisine was evaluated as an in vivo ligand for nAChR. Distribution of the radiotracer in brain and competition assays indicated that cytisine, appropriately labeled with a positron-emitting radionuclide, may be useful for study of nAChR by emission computed tomography.

Ritz MC, Mantione CR, London ED. Spermine interacts with cocaine binding sites on dopamine transporters. Psychopharmacology 1994;114:47-52.

Flesher JE, Scheffel U, London ED, Frost JJ. In vivo labeling of nicotinic cholinergic receptors in brain with [H-3]cytisine, Life Sci 1994;54:1883-1890.

Ingram DK, Spangler EL, Iijima S, Kuo H, Bresnahan EL, Greig NH, London ED. New pharmacological strategies for cognitive enhancement using a rat model of age-related memory impairment, Ann NY Acad Sci 1994;717:16-32.

London ED, Mukhin A. Polyamines as endogenous modulators of the N-methyl-D-aspartate receptor, Ann NY Acad Sci, in press.

Ingram DK, Spangler EL, Iijima S, Ikari H, Kuo H, Greig NH, London ED. Rodent models of memory dysfunction in Alzheimer's disease and normal aging: Moving beyond the cholinergic hypothesis, Life Sci, in press.

Shimada A, Spangler EL, London ED, Ingram DK. Spermidine potentiates dizocilpine-induced impairment of learning performance by rats in a 14-unit T-maze, Eur J Pharmacol, in press.

Bell JA, CL Beglan, and ED London: Paradoxical effect of ascorbic acid on NMDA-induced neurotoxicity, NeuroReport, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00328-07 CDM

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Pharmacokinetics and Pharmacodynamics of Drugs of Abuse in Hair

PRINCIPAL INVESTIGATOR

P.I.	E.J. Cone	Chief	Clinical Pharmacology Branch
	W.D. Darwin	Chemist	Clinical Pharmacology Branch
	D. Yousefnejad	Chemist	Clinical Pharmacology Branch

COOPERATING UNITS

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Chemistry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Drug residues have been detected in human hair specimens by a variety of analytical techniques. These reports have generated substantial interest in using hair as a historical record of drug usage. Current studies are designed to determine the presence and time course of drugs of abuse in human hair.

Healthy male volunteers with a history of chemical substance abuse participated in the study. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Subjects resided on the clinical ward of the ARC. Head and facial hair specimens were obtained prior to and after administration of drugs of abuse. Blood, saliva and urine specimens also were obtained. Analyses of tissue and biofluids for drug was performed by radioimmunoassay and gas chromatography/mass spectrometry.

These studies provide the scientific basis for determination of the usefulness of hair as a "historical record" for substance abuse.

PUBLICATIONS

Cone, E. J., Darwin, W. D. and Wang, W., The Occurrence Of Cocaine, Heroin And Metabolites In Hair Of Drug Abusers. Forensic Sci. Int., 63: 55-68, 1993.

Wang, W.L., Darwin, W.D. and Cone, E.J. Simultaneous Assay of Cocaine, Heroin And Metabolite In Hair, Blood, Saliva And Urine By Gas Chromatography-Mass Spectrometry. J. Chromatogr., in press, 1994.

Cone, E.J. and Wang, W.L. How Environmental Drug Exposure Can Impact Hair Testing for Drugs of Abuse. NIDA Monograph, In Press, 1994.

Wang, W.L. and Cone, E.J. Testing Human Hair for drugs of Abuse, IV. Environmental Cocaine Contamination And Washing Effects. Forensic Sci. Intl., In Press, 1994.

Goldberger, B.A., Darraj, A.G., Caplan, Y.H. and Cone, E.J. Detection Of Methadone, Methadone Metabolites, And Other Illicit Drugs Of Abuse In Hair Of Methadone Treatment Subjects. NIDA Monograph, In Press, 1994.

Goldberger, B.A., Caplan, Y.H. and Cone, E.J. Significance Of Detection Of Heroin And 6-Acetylmorphine In Hair. NIDA Monograph, in press, 1994.

Wang, W.L. and Cone, E.J. Testing Human Hair for Drugs of Abuse, V. Attempted Differentiation Of Environmental Cocaine Contamination From Active Cocaine Use. NIDA Monograph, in press, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00329-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Analysis of Data from the National Comorbidity Survey

PRINCIPAL INVESTIGATOR

P.I. J.C. Anthony, Ph.D. Sr. Staff Fellow Etiology Branch

COOPERATING UNITS

R. Kessler, Univ. of Michigan
L.A. Warner, Univ. of Michigan

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.2	0.19	0.01

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

This project seeks to assess the frequency and occurrence of drug dependence syndromes in the non-institutionalized population of the United States, age 15-54 years old, and to test hypotheses about suspected prevalence correlates and risk factors for drug dependence. As such, the project complements and strengthens information on psychoactive drug use that can be derived from the National Household Survey on Drug Abuse.

The first part of this project has involved statistical analyses of the survey data in order to estimate prevalence of drug dependence (by drug type), and the proportion of drug users who had become drug dependent (also by drug type). The data for these analyses derived from confidential interviews with 8,098 survey respondents, who had been selected by probability sampling to serve as a nationally representative sample of 15-54 year old Americans, and who then were recruited for the survey's diagnostic assessments. These analyses were extended to include tests of hypotheses about correlates of prevalence of drug dependence in the U.S. population, which have provided clues about suspected risk factors. As a result of this work, for the first time we have national estimates for the prevalence of drug dependence syndromes, and we have been able to make comparisons across specific drug types, based on data from a nationally representative sample. The results also have provided important confirmation of some previous findings about sociodemographic correlates of drug dependence. For example, African-Americans were no more likely than White Americans to have become drug dependent, with or without statistical adjustment for socioeconomic differences between these population sub-groups. Further, against a backdrop of generally higher prevalence values for men versus women, it was important to note higher female prevalence of dependence on sedative-hypnotic-anxiolytic drugs among women of middle age.

In on-going analyses of these data, we are investigating these cohort differences in prevalence of drug dependence in more detail; we are testing hypotheses about the age of onset of drug use and the risk of later drug problems; and we are attempting to understand the natural history or clinical course of treated and untreated drug dependence in relation to characteristics such as education and occupation

Anthony JC, Warner LA, and Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Experimental and Clinical Psychopharmacology. 2(3):1-25, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00330-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Early Adaptation and Developmental Outcome in Drug Exposed Infants

PRINCIPAL INVESTIGATOR

P.I.	C.E. Johanson, Ph.D.	Chief	Etiology Branch
	P.E. Suess, Ph.D.	IRTA	Etiology Branch
	E.J. Cone, Ph.D.	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

D. Svikis, Ph.D. Ctr.for Addiction in Pregnancy
L. Jansson, M.D. Crt. for Addiction in Pregnancy

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

This study will assess the functioning of drug exposed infants within the context of their unique environments (living with a drug using caretaker) and their own characteristic abilities to adapt. Early measures of the newborns' neurobehavioral and emotional adaptability along with maternal and environmental factors will be related to outcome measures of physiological, behavioral, emotional, and cognitive functioning during the second half of the first year of life. The specific functions targeted include the infants' abilities to regulate their arousal and reactivity to stimulation, and their development of emotional expressivity, attentional capacity, motivation, and visual recognition memory (an early predictor of intellectual functioning).

One hundred drug exposed, and one hundred non-exposed full-term newborns will be recruited at delivery. Verification of group classification will be determined by 1) examination of prenatal medical records and 2) meconium analysis. The infants will be tested as newboms and again at 1, 4, 6, 9 and 12 months. Assessments will include measures of neurobehavioral functioning, autonomic regulation and reactivity to stimulation (vagal tone, heart rate and cortisol), emotional regulation during mother-infant interactions, mastery motivation and attention during structured play with mother and examiner, Fagan Test of Infant Intelligence, and Bayley Developmental Scales. Maternal assessments include interviews, questionnaires, and observations for drug history and socio-economic factors, parenting attitudes, home and family environment, psychological and intellectual functioning, and maternal interactive and caretaking behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00331-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Association between Illicit Drug Use and Behavioral Repertoire in Adolescents

PRINCIPAL INVESTIGATOR

P.I.	C.E. Johanson, Ph.D.	Chief	Etiology Branch
	J.C. Anthony, Ph.D.	Sr. Staff Fellow	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Behavioral alternatives are among the determinants of drug use that have received attention in laboratory-based animal and human studies. The underlying notion is that availability of competing alternative reinforcers decreases drug-seeking behavior maintained by a drug reinforcer. This strategy is part of behavioral treatments that encourage patients to broaden their behavioral repertoire as a means of decreasing the reinforcing effects of drugs. To investigate this notion from a complementary perspective, we analyzed data from an epidemiologic sample of more than 1500 urban middle-school students, who had completed private interviews/questionnaires in Spring 1993 as part of a longitudinal field trial being conducted by the Johns Hopkins Prevention Research Center in collaboration with the Baltimore City Public Schools. The assessment included a questionnaire to assess current behavioral repertoire. Drawing upon a dichotomous variable factor analysis of the repertoire data, we constructed seven indicators to represent different behavioral domains and then used multiple logistic regression to estimate associations with illicit drug use, holding constant age and sex. Illicit drug use was associated independently with less involvement in religious activities and greater involvement in work and other adult-like roles. These results corroborate other evidence on the potential etiologic significance of behavioral repertoire in relation to the risk of illicit drug use. Since these results do not address issues of temporal sequencing or other limitations of cross-sectional data, the association will be reexamined in the continuing study of this epidemiologic sample. More specifically, it will be possible to determine the association of behavioral repertoires with initiation of drug use. In addition, a more complete analytic model may reveal interactions among the behavioral domains as well as the influence of other risk or protective factors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00332-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

The Effects of Expectations on Stimulant and Sedative Discriminations

PRINCIPAL INVESTIGATOR

P.I.	C.E. Johanson, Ph.D.	Chief	Etiology Branch
	K. Preston	Chief	Treatment Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.2	0.2	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Investigators who conduct studies designed to assess familial transmission of a vulnerability or resistance to drug abuse often interpret some of their findings as evidence of a genetic determinant. Families not only share genes but they also share an environment. Parents influence their children through modeling and the establishment of acceptable norms of behavior. This may include the formation of expectations about the effects of drugs. This study is designed to determine whether instructions can alter the mood effects of test drugs. The study consists of two experiments. In both, participants are trained to discriminate between 75 mg tripelennamine and placebo. In the first experiment, they are told that the capsules they receive might be a sedative, stimulant or placebo but that one of them is more sedative-like than the other. They are also informed that their discrimination will occasionally be tested, mostly with sedatives. These instructions are designed to bias the subject to report sedative-like effects. The second experiment is identical except that the instructions are designed to bias the subject to report stimulant-like effects. During both experiments, 4 drugs/doses will be tested: 2.5 and 5 mg diazepam and 5 and 10 mg d-amphetamine. It is expected that during the first experiment these low doses of diazepam, which previous studies have shown do not have robust sedative-like effects, will be identified as tripelennamine and clearly labeled as a sedative. Likewise, the malleable effects of amphetamine seen in previous studies should result in most subjects identifying at least the 5 mg dose as sedative-like. In contrast during the second experiment, it is more likely that a test drug will be identified as placebo and labeled as a stimulant. To date, 7 participants have completed both experiments with an additional two completing the stimulant experiment only and an additional one who completed the sedative experiment only. Preliminary analyses of the data indicate that discrimination and drug labeling results are consistent with the hypotheses.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00333-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

The Effects of Drugs on Brain Function

PRINCIPAL INVESTIGATOR

P.I.	C.E. Johanson, Ph.D.	Chief	Etiology Branch
	E. London, Ph.D.	Chief	Neuroscience Branch
	C. Schutz, M.D.	Visiting Fellow	Etiology Branch
	E. Cone, Ph.D.	Chief	Clinical Pharmacology Branch
	R. Pickens, Ph.D.	Senior Scientists	Office of the Director
	C. Contoreggi, M.D.	MRI	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	0.9	0.1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

There are large differences in the extent to which individuals abuse drugs, even when exposures are comparable. There are also differences in the effects drugs produce in individuals. It is not known, however, the extent to which an individual's propensity to abuse a drug, or self-administer it repeatedly, is related to the effects it produces. This study is designed to elucidate this relationship in order to increase our understanding of the mechanisms underlying individual differences in vulnerability to drug abuse. In the first part, subjects will participate in a 9-session self-administration experiment with 15 mg d-amphetamine and placebo, both administered orally. After sampling each of these two drugs during the first four sessions, subjects will be given a choice between them on five separate sessions. The degree of preference is measured by the number of times drug is chosen over placebo. In a second phase. changes in brain metabolism as assessed by PET and changes in brain electrophysiological activity in response to oral amphetamine in comparison to placebo will be assessed in order to correlate these effects with preference. Family history of drug use will also be determined and correlated with preference. To determine if any observed differences between those who tend to choose amphetamine and those who do not are due to the bioavailability of amphetamine, a third part will assess the pharmacokinetics of oral amphetamine in relationship to preference. Differences in hormonal responses will also be determined during this third part of the study. This study will help determine whether differences in propensity to self-administer a drug, which may indicate a vulnerability to drug abuse, are related to specific effects of the drug.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00334-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Conditioned Effect of Placebo Associated with Different Reinforcement Conditions

PRINCIPAL INVESTIGATOR

P.I.	C.E. Johanson, Ph.D.	Chief	Etiology Branch
	C.R. Schuster, Ph.D.	Senior Scientists	Office of the Director
	A. Mattox, Ph.D.	IRTA	Office of the Director

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The ability of placebo drug capsules to serve as conditioned reinforcers as a function of being paired with differential rates of point reinforcement was evaluated. Normal volunteers were administered two differently colored capsules orally in separate sessions. Although different in color, both capsules were placebos. The volunteers were told that these capsules might contain a stimulant, sedatives, or placebo. During each session, the volunteers participated in performance tasks. Subjective effects and physiological measures were also obtained. The tasks, which were difficult and ambiguous, were programmed so that following the administration of one color capsule, the frequency of reinforcement was markedly greater than following the administration of the capsule of the other color. Volunteers were told that the difference in point earnings was related to the accuracy of their performance. During the first experiment, participants were exposed two times each to the two reinforcement conditions. During choice sessions, no performance tasks were done but participants were offered the opportunity to choose which capsule they preferred to self-administer. During the exposure sessions, there were large differences in the mood effects associated with the two capsules and the reinforcement conditions. During choice sessions, most participants chose the capsule associated with the high frequency of reinforcement. A second experiment was designed to determine whether the differential mood effects associated with the differential reinforcement conditions could be conditioned to the color of the placebo capsule associated with them. Although similar differences in mood were seen during sessions when performance testing was done, there were no differential mood effects observed when the two different colored capsules were administered in the absence of performance testing. These results indicate that drugs may function as conditioned reinforcers and thus influence the probability of drug-taking behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00335-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Major Depression in the Teen Years

PRINCIPAL INVESTIGATOR

P.I.	C.E. Johanson, Ph.D.	Chief	Etiology Branch
	J.C. Anthony, Ph.D.	Sr. Staff Fellow	Etiology Branch
	A. Gupman, Ph.D.	Social Science Analyst	Etiology Branch
	H. Chilcoat, Ph.D.	Staff Fellow	Etiology Branch
	C. Schutz, M.D.	Visiting Fellow	Etiology Branch

COOPERATING UNITS

S. Kellam, Ph.D., Johns Hopkins

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	0.5	2.5

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

The purpose of this collaborative study is to provide a definitive and conclusive diagnosis of depression of adolescent children who reported high levels of depressive symptoms in a lay-administered questionnaire during the first-stage sampling of children in a local school system. In addition, a representative sample of children was also assessed as a control. These children, who were between 12 and 14 years old, have participated in a longitudinal study since entering first grade. Each year they have been assessed on a variety of dimensions including mental health, school achievement, drug use, and family life. In addition, during the first two years of school, an intervention aimed at decreasing depression and drug use in adolescence was given. After the first-stage sampling, children who agreed to participate came to the Prevention Research Center for a 2 to 3 hr interview along with a parent. At that time, they were administered the K-SADS plus some additional diagnostic instruments including the CIDI. The mother was interviewed as well as part of the K-SADS assessment. The interviews were videotaped and the tapes will eventually be used by a group of clinicians to make a consensus diagnosis.

A total of 202 letters were mailed. Of these, 136 were selected because the student had scoring positively for depression during the spring assessment. An additional 66 students were randomly selected as controls. Of these 202 families, we were able to contact 167 families by phone, and, of those, 116 were interviewed (70%). Currently, extensive analyses of the data are being conducted. These analyses will include: 1) a quantitative assessment of the test-retest reliability of the CIDI, and 2) a comparison of both CIDI's and the K-SADS. In order to establish a definitive DSM-IIIR diagnosis, a team of clinicians is being formed to co-evaluate the videotaped K-SADS interviews. It is likely that a host of additional analyses will be conducted, even using data from future assessments in this ongoing longitudinal study.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00336-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Family Structure and Initiation of Illicit Drug Use among Adolescents

PRINCIPAL INVESTIGATOR

P.I.	C.E. Johanson, Ph.D.	Chief	Etiology Branch
	J.C. Anthony, Ph.D.	Sr. Staff Fellow	Etiology Branch

COOPERATING UNITS

T. Suh, Johns Hopkins

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

This study was designed to evaluate the association between family structure and the initiation of illicit drug use among a representative sample of 12-17 year old adolescents. The hypothesis was that adolescents who do not live with either their mother or father might are at an increased risk for starting illicit drug use. This hypothesis was tested using an incident case-control analyses of self-report data from the 1992 National Household Survey on Drug Abuse. A post-stratification procedure was used to hold constant shared neighborhood characteristics. Multiple logistic regression models were used to estimate relative risk of initiating illicit drug use among adolescents residing in homes with varying kinds of parents present, holding constant age, sex, ethnicity, family income, and number of siblings. A total of 433 incident cases and 1830 neighborhood-matched controls were identified. The risk of starting illicit drug use was highest for father alone families, followed by mother/stepfather families, no-parent families and lowest for mother/father families. Mother alone and father/stepmother families did not show any significantly higher risk than mother/father families.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00337-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Etiologic Pathways in the Development of Parent Monitoring

PRINCIPAL INVESTIGATOR

P.I.	H. Chilcoat, Ph.D.	Staff Fellow	Etiology Branch
	C.E. Johanson, Ph.D.	Chief	Etiology Branch

COOPERATING UNITS

N. Breslau, Henry Ford Hospital

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	1	2

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Parental monitoring and supervision of a child's behaviors in and out of the home have been identified in a number of cross-sectional and longitudinal studies as factors that are strongly associated with early drug use initiation and later, more problematic use. Although there is evidence to suggest that parent monitoring plays a causal role in the development of drug use, it is important to begin to examine factors that influence parent monitoring itself. This is particularly important for intervention trials targeting parent monitoring, which require a large investment and are likely to be more successful if an appreciation of the determinants of parent monitoring are understood. The focus of the present study is to examine the potential role of parental drug use and psychiatric symptomatology on parenting behavior and more specifically, parent monitoring. Telephone interviews are being conducted with parents of 823 8 -11 year old children. These children originally participated in a concurrent prospective study of the developmental outcome of children of low birthweight sampled from urban and suburban Detroit hospitals. When these children were six, they completed neuropsychologic testing and neurologic examinations. The NIMH-DIS was used to measure DSM-IIIR psychiatric and substance abuse disorders in the mother. In addition, maternal IQ, family demographic characteristics, family psychiatric history, and family social environment were measured. These children are being re-interviewed as they reach age 11 to assess involvement in drug use and suspected risk factors. By collaborating in this study and adding the assessment of parent monitoring, there is an opportunity to: 1) replicate previous studies on the role of parent monitoring on child's drug use, and 2) to examine prospectively factors that have influenced present-day level of parent monitoring. Statistical analyses will be conducted to compare level of parenting across strata of the measures that were obtained four years previously, namely parent drug use and psychiatric symptomatology, and then to determine the subsequent relationship of parent monitoring to the child's drug use initiation. To date, 350 of the interviews have been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00338-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Age-specific Trends in the Prevalence of Hallucinogen Use from 1988-1992

PRINCIPAL INVESTIGATOR

P.I.	H. Chilcoat, Ph.D.	Staff Fellow	Etiology Branch
	C. Schutz, M.D.	Visiting Fellow	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Much concern has developed recently over the possible increase in hallucinogen use among children and young adults, as some researchers warn about a possible resurgence of use of these drugs. In particular, the Monitoring the Future Study, using a survey administered in schools, found a statistically significant increase from 1991-1992 in the lifetime and one-year prevalence of hallucinogen use among eighth-graders, as well as an increasing trend for all age groups through young adulthood. We set out to see if similar patterns of hallucinogen use could be observed using data from three National Household Surveys on Drug Abuse conducted in 1988, 1990, and 1992. We employed Generalized Additive Models (GAM) to examine the age-specific prevalence of hallucinogen use in the lifetime and past year. These models use a smoothing technique to account for non-linearity in prevalence across the age range while maximizing precision. We found no evidence of an increasing trend in the one-year or lifetime prevalence of hallucinogens over the last four years. In each of the surveys, 19 year olds were most likely to have used in the last year; however, there is no evidence that this use continues as these cohorts age into their twenties. These results indicate that the recent alarm over hallucinogen use should be tempered and that focus on this class of drugs should not distract attention from other drugs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00339-01 CTS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Factors Associated with Seeking Drug Abuse Treatment in Frequent Cocaine Users

PRINCIPAL INVESTIGATOR

P.I.	I.D. Montoya, M.D.	Visiting Fellow	Treatment Branch
	C. Schutz, M.D.	Visiting Fellow	Etiology Branch
	H. Chilcoat, Ph.D.	Staff Fellow	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Treatment Branch

SECTION

Clinical Trials

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

To determine the psychological and drug use factors associated with seeking drug abuse treatment in the general population, we studied a sample of cocaine users (n=626) , who reported cocaine use at least once monthly, from the annual NIDA National Household Survey on Drug Abuse conducted in both 1991 and 1992 (N≈60,000).

We compared a group of 117 individuals who sought treatment (ST) with a group of 509 individuals who did not seek treatment (NST), during the past year. The ST had 58.1% males, 36.8% Whites, 41% African Americans, 21.4% Hispanics, 90.6% graduated from high school, and 17.1% were married. They did not differ significantly from the NST in these socio–demographic characteristics. The ST had significantly ($p<.001$) higher odds of heroin (relative odds [RO] = 3.3), cigarette (RO=2.6), or crack (RO=2.3) use during the past year. There were no differences in alcohol, inhalant, hallucinogen, marijuana, or PCP use during the past year. The relative odds of seeking treatment between individuals who used cocaine daily and those who used once or twice monthly was 6.6. The ST had significantly ($p<.0001$) more social and behavioral problems related to the use of cocaine or other drugs. The ST reported significantly more problems such as depression (RO=6.7), arguments (RO=5.2), loneliness (RO=4.6), anxiety (RO=3.7), cocaine withdrawal (RO=4.9), or feeling dependent on cocaine (RO=5.4).

Previous reports attempting to differentiate drug abusing individuals who seek treatment have failed to find differences because they relied heavily on treatment based samples. This is the first study based on a representative sample of the U.S. general population that shows that frequent cocaine users who seek treatment are at higher distress than those who do not seek treatment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00340-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Neighborhood Deterioration and Early Initiation of Drug Use

PRINCIPAL INVESTIGATOR

P.I.	C. Schutz, M.D.	Visiting Fellow	Etiology Branch
	H. Chilcoat, Ph.D.	Staff Fellow	Etiology Branch
	J. Anthony, Ph.D.	Sr. Staff Fellow	Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Early initiation of drug use has be shown to be associated with increased risk of later drug abuse and development of drug dependence. The hypothesis tested in this four wave longitudinal study of urban schoolchildren, conducted in Baltimore MD concerned a suspected causal association between neighborhood deterioration and the risk of early initiation of drug use. A total of 925 participants completed four confidential standardized interviews conducted by specially trained interviewers in the spring of four successive years. In addition to drug use assessment, separate standard scales were applied to measure an array of risk factors, including neighborhood deterioration, peer drug use, parental supervision and antisocial behavior. By 1992, a total of 340 youths, then 12-14 years old, reported drug involvement (smoking tobacco, using alcohol without parental permission, use of inhalants, marijuana, or cocaine). An analysis using Kaplan-Meier curves showed that throughout the follow-up interval children reported earlier onset of drug use in areas rated more deteriorated (log rank test with 2 d.f.: 11.59, p-value: 0.003). Under the Cox proportional hazards model, holding constant other factors (peer drug use, parent monitoring, antisocial behavior, etc.), this association still persisted, resulting in a hazard ratio of 1.58 between the lowest and highest tertile of neighborhood deterioration (95% CI: 1.13-2.23). Thus, neighborhood deterioration appeared to be associated with early onset of drug use independent from other suspected factors. We plan to extent this investigation and use geographical software (GIS) to include census tract information, which we now have available.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00341-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Risk Factors for Starting Illicit Drug Use among Youths with No Conduct Disorder

PRINCIPAL INVESTIGATOR

P.I. C. Schutz, M.D. Visiting Fellow Etiology Branch

J. Anthony, Ph.D. Sr. Staff Fellow Etiology Branch

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

There is a substantial body of research into childhood misbehavior and conduct disorder (CD) as explanations for illicit drug use, but less attention to the issue of whether risk factors for illicit drug use might vary by level of CD. We have started to investigate this issue by testing specifically for epidemiologic evidence that earning pay at a job or assuming other adult-like roles might signal an increased risk of starting illicit drug use among youths with no CD or no more than minimal CD. These hypotheses were tested by conducting incident case-control analyses of self-report data gathered from 12-17 year olds sampled for the 1992 National Household Survey on Drug Abuse. Youths were excluded if they reported any positive responses to 11 questions on CD or if they reported starting illicit drug use more than 1 year ago. We used post-stratification to hold constant shared neighborhood characteristics and multiple logistic regression models to estimate relative risk of starting illicit drug use in relation to the suspected risk factors. Out of 5123 youths at risk, we were able to match 162 incident cases who recently had started illicit drug use with 722 neighborhood controls. Adjusting for demographic factors, starting illicit drug use was independently associated with working for pay. There was some evidence implicating other adult-like roles. A parallel investigation of adolescents with at least one symptom of conduct disorder revealed the lack of association between starting illicit drug use and working for pay. These findings are compatible with previous empirical research on the costs and benefits of adolescent work. This research indicated that there is a number of negative outcomes associated with adolescent work. In additional analyses, we will examine similarities and differences in the profiles of risk factors for illicit drug use among youth with and without CD.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00342-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Inhalant Use as a Vulnerability Marker for Heroin Use

PRINCIPAL INVESTIGATOR

P.I. C. Schutz, M.D. Visiting Fellow Etiology Branch

COOPERATING UNITS

E. Johnson, Ph.D. Johns Hopkins

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

In a previous study we demonstrated that inhalant use is a good vulnerability marker for injecting drug use. The study was based on the National Household Survey on Drug Abuse. The major restriction of our findings were that the analyses were based on a survey with cross-sectional character. As a follow-up to that study, we are currently analyzing data from a recently completed longitudinal study. A cohort of African American school children have been followed from first grade to tenth grade. Sixteen years later 82% of those children, now approximately 32 years of age, have been re-interviewed. These follow-up data allow us to test our hypothesize that those who used inhalants during their youth are at a greater risk for use of heroin, allowing for a clear evaluation of time sequence. After elimination of those respondents who used heroin as adolescents and those with missing responses, we were left with 698 respondents. Preliminary analyses indicate that after adjustment for sociodemographic factors and adjustment for use of marijuana, inhalant use was a significant predictor of later heroin use (RR: 7.6, 95% CI: 1.73-33.27). In the same model we found use of marijuana also to be a predictor with a slightly lower point estimate of RR = 5.4 (95% CI of 1.84-15.85). None of the sociodemographic factors was significantly associated with later heroin use. These findings strengthen our argument that early inhalant use deserves more attention, not only because of toxicity associated with long and short term exposure, but also as a vulnerability marker for increased risk of injected drugs such as heroin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00343-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Morphine-Induced Activity and DA in the Nucleus Accumbens in Inbred Rat Strains

PRINCIPAL INVESTIGATOR

P.I.	C. Schutz, M.D.	Visiting Fellow	Etiology Branch
	E. Ambriosio, Ph.D.	Visiting Fellow	Preclinical Pharmacology Laboratory
	T. Shippenberg, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	G. Elmer, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	C. Heidreder, Ph.D.	Visiting Fellow	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.2	1	0.2

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Two inbred rat strains, the Lewis and Fischer 344, differ in certain of their behavioral responses to remains unclear. However, biochemical differences within the mesolimbic dopamine (DA) system of these strains have been reported. In the present study, the effects of acute morphine challenges on DA overflow in the NA were studied using in vivo microdialysis in the freely moving rat. Locomotor activity was studied in separate groups of rats. We found that basal DA release was slightly, but significantly, higher in Fischer rats, compared to Lewis rats. Neither saline nor the 1.0 mg/kg dose of morphine modified DA release in the NA. At 5.0 mg/kg, however, a significant increase in DA overflow was measured. DA release was markedly higher in Fischer rats at the 10 to 40 min interval with a peak increase of 553% at 30 min. In contrast, the peak increase in Lewis rats (336%) occurred at the 20 min time point. There was no significant difference between strains in locomotor activity during the habituation test. However, the time course of morphine's effects differed between the two strains. At present, it is not clear if pharmacokinetic or pharmacodynamic alterations explain these differences.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00344-01 VUL

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Treatment Entry among a Community Wide Sample of IDUs

PRINCIPAL INVESTIGATOR

P.I.	C. Schutz, M.D.	Visiting Fellow	Etiology Branch
	J. Anthony, Ph.D.	Sr. Staff Fellow	Etiology Branch

COOPERATING UNITS

E. Rapiti, Latium Regional Authority
D. Vlahov, Johns Hopkins

LAB/BRANCH

Etiology Branch

SECTION

Vulnerability

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Most etiologic studies on drug use, specially on injecting drug use, are based on treatment samples. This study aimed to clarify some potential differences between treated and untreated drug users that might be considered in studies that only have drug users recruited from treatment settings as participants. This study further shed light on different suspected determinants of entry into a detoxification treatment only and entry into a methadone maintenance treatment program. Our analysis were based on baseline and six-month follow-up interviews of initially 2,879 injecting drug users (IDUs), who had been recruited through extensive community outreach. We first examined characteristics associated with being in treatment at baseline and up to one year before baseline. A further investigation was focused on active injecting drug users, who had not been in treatment in that time period, and who returned for follow-up assessment within 9 months after baseline. We studied hypothesized determinants of those who entered a detoxification treatment, and those who entered a methadone maintenance program, comparing them to active IDUs who did not enter these treatments. Of 1,039 drug users, who reported injecting drugs at the time of the follow up interview, a total of 144 entered a detoxification program, a total of 64 entered a methadone maintenance treatment program. Multiple regression analysis indicated that enrollment in a detoxification program was associated with a recent episode of drug overdose, recent higher frequency of injecting drugs, and a history of arrest or treatment. Being married or living with a partner, female sex, long duration of drug use (>10 years), and a history of treatment had separate associations with enrollment into a methadone maintenance treatment program.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00345-01 BPGS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Genetic Factors in Drug Self-Administration

PRINCIPAL INVESTIGATOR

P.I.	Gregory Elmer, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory
	Steven Goldberg, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Richard Rothman, M.D., P	Chief	Clinical Pharmacology Branch
	Toni Shippenberg, Ph.D.	Sr. Staff Fellow	Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Behavioral Pharmacology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.45	0.95	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

A major research emphasis in our laboratory has been to investigate genetic influences on intravenous opioid self-administration behavior in inbred rat and mouse strains. Recent hypotheses regarding the role of innate locomotor activity in the acquisition of drug-reinforced behavior are amenable to testing using this behavior genetics approach. Studies were conducted to investigate the relationship between drug-naive behaviors and the rate of acquisition and extinction of opioid-reinforced behavior. Operant drug-reinforced behavior was examined in a 24 hr access paradigm in which rats received 1 mg/kg/inj of morphine per operant response. The results of these studies suggest large genetic differences in the rate of acquisition and extinction of morphine self-administration that was significantly correlated with baseline locomotor activity. Initial studies using inbred mouse strains confirm these studies and suggest an inverse correlation between the amount of behavior maintained by 1 mg/kg/inj morphine and the potency and rate of tolerance to morphine's analgesic effects in four inbred mouse strains. Additional studies investigating the acute behavioral effects of drugs that may influence subsequent reinforcing properties are being investigated using a chronic drug sensitization paradigm and a conditioned drug effect paradigm. Thus far, pilot studies suggest that sensitization to cocaine's locomotor effects and the conditioned locomotor activity effects of a drug differ in a genotype-dependent manner predictive of self-administration behaivor. The biochemical differences underlying vulnerability to acquisistion and resistance to extinction of drug self-administration behavior are being pursued in collaboration with Drs. Shippenberg, Heidbreder and Schutz using an in vivo microdialysis technique and Dr. Rothman using a conditioned sensitization paradigm. Naive and morphine-induced efflux of dopamine were compared in two inbred rats strains that demonstrate fast and slow rates of acquisisition of morphine self-administration behavior, the Lewis and F344 strains, respectively. Dopamine efflux in the nucleus accumbens of the Lewis rats was relatively unaffected by acute morphine administration as compared to the F344 rats. These data are in contrast to previously reported differences in a randomly outbred rat population.

Uhl GR, Elmer GI, LaBuda MC, Pickens RW. Genetic influences in drug abuse. In: Meltzer HY, ed. Psychopharmacology: The fourth generation of progress. New York: Raven Press, 1994; in press.

Elmer GI, Pieper JO, Goldberg SR, George FR. Opioid operant self-administration, analgesia, stimulation and respiratory depression in μ-deficient mice, Psychopharmacology 1994; in press.

Ambrosio E, Goldberg SR, Elmer GI. Behavior genetic analysis of innate locomotor activity and acquisition of morphine self-administration behavior, Behavioral Pharmacology 1994; in press.

Elmer GI, Goldberg SR, Gorelick DA, Rothman RB. Genetic factors involved in the acute sensitivity and context-specific sensitization to cocaine, Psychopharmacology 1994; in press.

Sudakov SK, Goldberg SR, Borisova EV, Surkova LA, Turina IV, Rusakov DJ, Elmer GI. Differences in morphine reinforcement property in two inbred rat strains: associations with cortical receptors, behavioral activity, analgesia and the cataleptic effects of morphine, Psychopharmacology 1993;112:183-8.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00346-01 CNG

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Dopamine D2 Receptor-Induced Responses

PRINCIPAL INVESTIGATOR

P.I.	Roy Pickens, Ph.D.	Senior Scientist	Office of the Director
	George Uhl, M.D., Ph.D.	Act. Scientific Director	Office of the Director
	Richard Rothman, M.D., P	Chief	Clinical Pharmacology Branch
	Johanathan Katz, Ph.D.	Chief	Preclinical Pharmacology Laboratory
	Michael Bauman, Ph.D.	Staff Fellow	Clinical Pharmacology Branch

COOPERATING UNITS

Michele LaBuda, Ph.D., Johns Hopkins

LAB/BRANCH

Office of the Director

SECTION

Clinical Neurogenetics

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	1	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☒ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

Rationale: In 1990, Blum and associates reported an allelic association between the D2 dopamine receptor gene and alcoholism. A Taq I restriction fragment length polymorphism (RFLP) located in the 3' flanking region of the gene was found to be more common among alcoholics (69%) than nonalcoholics (20%) [Blum et al., 1990]. This same allele (A1) has now been associated with other types of substance use [Smith et al., 1992], while another variant of the D2 receptor gene (B1 allele), located more towards the 5' region of the gene, has also been associated with alcoholism and other drug abuse [Blum, 1992].

To further clarify the role of these allelic associations in susceptibility to addiction, parameters will be developed that distinguish individuals who differ in expression of D2 alleles. Since dopamine D2 agonists have been shown to cause changes in neuroendocrine in humans [Ben-Jonathan, 1985] and to improve motor functioning and abnormalities in visual evoked potentials (VEP) in patients with Parkinson's disease Wachtel, 1991; Bodis-Wollner et al., 1986; Onofri et al. 1986], these will be examined as possible indicators of differences in dopamine D2 allelic status.

This protocol will serve two purposes. First, it will allow us to characterize changes in neuroendocrine response profile, visual evoked potential, and motor response in non-addicted individuals after administration of the dopamine D2 agonist pergolide. Second, it will allow us to test the hypothesis that individuals who differ in D2 alleles will have different patterns of responses after pergolide challenge. In the protocol, pergolide will be administered orally in low doses to normals without a history of drug dependence or recent illicit drug use, and will not be given in combination with any other drug.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00347-01 MNP

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Involvement of nitric oxide in drug-induced neurotoxicity

PRINCIPAL INVESTIGATOR

P.I.	Jean Lud Cadet, M.D.	Chief	Neuroscience Branch
	Peilin Sheng, Ph.D.	Visiting Fellow	Neuroscience Branch
	Catherine Cerruti, Ph.D.	Visiting Fellow	Neuroscience Branch

COOPERATING UNITS

LAB/BRANCH

Neuroscience Branch

SECTION

Molecular Neuropsychiatry

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

These studies examine the effects of methamphetamine (METH) in an in vitro model of rat fetal mesencephalic cells. In addition, we sought to determine if production of nitric oxide was involved in the neurotoxic events associated with the presence of METH in the culture medium. In mesencephalic primary DA cultures, METH (1.5 mM) caused a significant reduction of neurons. Tyrosine hydroxylase (TH) immunohistochemistry showed a marked reduction of TH-positive cells with normal architecture. METH-induced toxic effects were significantly attenuated in the presence of inhibitors of nitric oxide synthase (NOS). Moreover, inhibitors of ADP-ribosylation such as benzamide and nicotinamide also blocks METH toxic effects in vitro. There was an associated increase in reactive gliosis in the presence of methamphetamine. reactive gliosis was also reduced in the presence of these inhibitors. These results suggest that NO formation might play an important role in the manifestation of METH-induced neurotoxicity. When taken together with our in vivo results using the superoxide dismutase transgenic mice, our data further implicate a role for oxidative stress in the manifestation of the deleterious effects of the amphetamines.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00348-01BPS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Role of opioid receptors in cocaine and opioid abuse

PRINCIPAL INVESTIGATOR

P.I. S. Izenwasser Sr. Staff Fellow Preclinical Pharmacology Laboratory

COOPERATING UNITS

LAB/BRANCH

Preclinical Pharmacology Laboratory

SECTION

Psychobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	0.5	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

These studies are designed to increase our understanding of the neurochemical mechanisms that are relevant to cocaine and opioid abuse. Cocaine and opioids such as morphine and heroin are widely abused substances that activate dopamine rich regions of the brain, and there are many studies suggesting involvement of opioid systems in the actions of psychomotor stimulants. Anatomical studies demonstrate that dopaminergic terminals are co localized with opioid receptors and opioid peptides in many brain regions. In animal models, cocaine induced reinforcement is attenuated by either dopamine or opioid antagonists, suggesting that both systems are involved in the effects of cocaine.

The specific objective of this project is to examine whether there are functional changes in opioid receptors in rat brain following treatment with cocaine, morphine, or opioid antagonists. Since opioid receptors are negatively coupled to adenylyl cyclase (opioids will inhibit cyclase activity), it is possible to measure changes in the function of opioid receptors in vitro. Chronic treatment with an opioid receptor antagonist, such as naltrexone, produces an increase in the number of mu opioid receptors in the brain. Recent studies in our laboratory have shown that there are also increases in the function of opioid receptors following chronic naltrexone administration. We have also shown that there are increases in these receptors following chronic, continuous administration with cocaine, but that these changes are limited to specific brain regions. Furthermore, the magnitude of the changes appear to be different following daily injections of cocaine (a treatment regimen that produced behavioral sensitization) than after continuous infusions of cocaine (a regimen that produced behavioral tolerance). These findings are being further investigated. These findings suggest that the opioid system may play an important role in the behavioral effects produced by cocaine and may serve as a target for the development of medical therapies for cocaine abuse.

Cote TE, Izenwasser S, Weems, HB Naltrexone induced upregulation of mu opioid receptors on 7315c cell and brain membranes: enhancement of opioid efficacy in inhibiting adenylyl cyclase. Journal of Pharmacology and Experimental Therapeutics, 1993;267:238 244.

Izenwasser, S. Increased mu opioid efficacy for inhibition of adenylyl cyclase induced by chronic treatment with naltrexone or cocaine. Regulatory Peptides, 1994; in press

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00349-01 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Mu Opiate and Related Receptors I: Human cDNA and Gene Structure

PRINCIPAL INVESTIGATOR

P.I.	J.B. Wang, M.D., Ph.D.	Guest Scientist	Molecular Neurobiology Branch
	Peter Johnson, Ph.D.	PRAT Fellow	Molecular Neurobiology Branch
	Antonio Persico, M.D.	Visiting Fellow	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

A.L. Hawkins, C.A. Griffin, Johns Hopkins
H. Xu, R. Rothman, Clinical Pharm. Branch

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.5	2.5	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Mu receptor distributions and pharmacologic properties place them among the receptors most identified with the analgesic and addicting properties of opiate drugs. In previous FYs, cDNAs encoding rodent mu opiate receptors have identified by our group. Availability of these cDNAs have allowed us to define the structure of the human mu opiate receptor cDNA and gene, identify human kappa opiate receptor cDNAs, identify closely-related "orphan" receptor cDNAs, and compare pharmacological features of mu opiate receptors between the human and rodent receptors. This work defines, for the first time, the structure of this primary site of opiate drug euphoria, addiction and analgesia in humans.

Wang J-B, Imai Y, Eppler CM, Gregor P, Spivak C, Uhl GR. mu Opiate receptor/binding protein: cDNA cloning and expression, PNAS 1993;90:10230-4.

Wang JB, Johnson PS, Persico A, Hawkins AL, Griffin CA, Uhl GR. Human mu opiate receptor: cDNA and genomic clones, pharmacologic characterization and chromosomal assignment, FEBS Lett 1994;338:217-22.

Johnson PS, Wang JB, Wang WF, Uhl GR. Expressed mu receptor couples to adenylate cyclase and phosphatidyl inositol turnover, NeuroReport 1994;5:507-9.

Uhl GR, Childers S, Pasternak G. An opiate receptor gene family reunion, TINS 1994;17:89-93.

Eppler CM, Hulmes JD, Wang J-B, Johnson B, Corbett M, Luthin DR, Uhl GR, Linden J. Purification and partial amino acid sequence of a mu opioid receptor from rat brain, J Biol Chem 1993;268:26447-51.

Rothman RB, Xu H, Wang JB, Partilla JS, Kayakiri H, Rice KC, Uhl GR. The ligand-selectivity of cloned human and rat opioid mu receptors are similar: A quantitative study with [1251]Ioxy-ago, Regul Pept 1994;in press.

Rothman RB, Xu H, Wang JB, Partilla JS, Kayakiri H, Rice KC, and Uhl GR. Ligand-selectivities of cloned human and rat opioid mu receptors, J Pharmacol Exp Ther 1994;submitted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00350-01 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Mu Opiate Receptors II: Structure/Function Relationships

PRINCIPAL INVESTIGATOR

P.I.	Christopher Surratt, Ph.D.	Senior Staff Fellow	Molecular Neurobiology Branch
	Peter Johnson, Ph.D.	PRATT Fellow	Molecular Neurobiology Branch
	Jia Bei Wang, M.D., Ph.D.	Guest Scientist	Molecular Neurobiology Branch
	Akiyoshi Moriwaki, Ph.D.	Visiting Fellow	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Mu opiate receptors are the principal brain sites for the analgesic, euphoric and addicting activities of morphine and heroin. Pharmacologic data suggest that these receptors contain binding sites for agonists and antagonists, incuding opiate "small molecule" drugs and larger neuropeptides, but details of the means whereby these receptor proteins recognize these ligands are currently unknown.

In the current FY, mutated, deleted, and chimeric versions of the rat and human mu receptors have been created and studied to refine our understanding of receptor/ligand interactions, and of receptor intrinsic activities and G-protein coupling. N-terminal involvement in binding appeared minimal; 64 N-terminal amino acids of the rat mu receptor could be removed without effects on radioligand binding. Further deletion of 33 C-terminal residues yielded a receptor which recognized mu-selective agonists morphine and DAMGO ([D-Ala2,MePhe4,Gly-ol5]enkephalin) at wild type levels. Three charged transmembrane residues of the mu receptor, Asp-114, Asp-147 and His-297, were critical for high affinity agonist recognition, suggesting possible ionc interactions with aspects of mu receptor radioligands. Results of studying chimeric mu/kappa receptors in which the putative second extracellular loop of the wild type mu receptor has been replaced with that of the kappa receptor fit with a substantial role for this extracelular loop in dynorphin peptide recognition.

These studies substantially enhance our working knowledge of means whereby opiate receptors recognize opiate drugs and opioid peptides, and provide significant clues to new pathways for formulation of selective new drugs with activities at these receptors.

Surratt CK, Johnson PS, Moriwaki A, Seidleck BK, Blaschak CJ, Wang JB, Uhl GR. mu Opiate receptor: charged transmembrane domain amino acids are critical for agonist recognition and intrinsic activity, J Biol Chem 1994;269(32):20548-53.

Wang JB, Johnson PS, Wu J-M, Wang WF, Uhl GR. Human k opiate receptor second extracellular loop elevates dynorphin's affinity for human mu/kappa chimeras, J Biol Chem 1994;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00351-01 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Mu Opiate Receptors III: Structure/Function and Second Messenger Effects

PRINCIPAL INVESTIGATOR

P.I.	Peter Johnson	PRATT Fellow	Molecular Neurobiology Branch
	Jia Bei Wang, M.D., Ph.D.	Guest Scientist	Molecular Neurobiology Branch
	Christopher Surratt, Ph.D.	Senior Staff Fellow	Molecular Neurobiology Branch
	Charles Spivak, Ph.D.	Pharmacologist	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

CM Eppler, American Cyanamid Co.

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Opiate receptors recognize endogenous opioid peptide neurotransmitters and exogenous opiate drugs of high abuse liability and analgesic benefits. Opiate receptors produce their effects in cells by altering intracellular G-protein linked second messengers and altering opening of G-protein-linked channels, especially those conducting potassium and calcium. In order to improve understanding these key elements in mediating opiate addictions, we have used cloned, mutant, deleted, and chimeric opiate receptor cDNAs to identify portions of the morphine-preferring mu opiate receptor that are important for coupling to second messenger systems.

Molecular cloning studies have identified cDNAs encoding each of the principal pharmacologically defined opiate receptors from several species. Expression of these cDNAs and their mutants in COS cells has revealed striking differences in coupling to G-protein-linked second messenger systems. Both human and rat muORs can mediate morphine and DAMGO inhibition of forskolin-stimulated adenyl cyclase activity in COS and/or CHO cell expression systems. In addition, morphine stimulates IP3 accumulation in cells expressing hmuOR. Mutagenesis has revealed the importance of charged transmembrane domain residues and the C-terminal 33 amino acids of the rmuOR for the intrinsic activity of the receptor. These results underscore the specificity of second messenger effects that can be observed in COS cell systems with members of this gene family.

Johnson PS, Wang JB, Wang WF, Uhl GR. Expressed mu receptor couples to adenylate cyclase and phosphatidyl inositol turnover, NeuroReport 1994;5:507-9.

Wang JB, Johnson PS, Persico A, Hawkins AL, Griffin CA, Uhl GR. Human mu opiate receptor: cDNA and genomic clones, pharmacologic characterization and chromosomal assignment, FEBS Lett 1994;338:217-22.

Wang JB, Johnson PS, Imai Y, Persico AM, Ozenberger BA, Eppler CM, Uhl GR. cDNA cloning of an orphan opiate receptor gene family member and its splice variant, FEBS Lett 1994;1994;348:75-9.

Surratt CK, Johnson PS, Moriwaki A, Seidleck BK, Blaschak CJ, Wang JB, Uhl GR. mu Opiate receptor: charged transmembrane domain amino acids are critical for agonist recognition and intrinsic activity, J Biol Chem 1994;269(32):20548-53.

Wang JB, Johnson PS, Wu J-M, Wang WF, Uhl GR. Human k opiate receptor second extracellular loop elevates dynorphin's affinity for human mu/kappa chimeras, J Biol Chem 1994;in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00352-01 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Mu Opiate Receptor IV: Distribution and Regulation

PRINCIPAL INVESTIGATOR

P.I.	Yasuo Imai, D.D.S, Ph.D.	Visiting Foriegn Fellow	Molecular Neurobiology Branch
	Akiyoshi Moriwaki, Ph.D.	Visiting Foreign Fellow	Molecular Neurobiology Branch
	Jia Bei Wang, M.D., Ph.D.	Guest Scientist	Molecular Neurobiology Branch
	Donna Walther, M.S.	Research Biologist	Molecular Neurobiology Branch
	Charles Spivak, Ph.D.	Pharmacologist	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
3.3	2	1.3

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The mu, or morphine preferring, opiate receptor is the receptor most identified with the addictive and analgesic properties of opiate drugs. Previous studies with antagonists have identified regulation of receptor binding properties and/or function following chronic opiate administration. For these reasons, the regional distribution and regulated expression of rat mu opiate receptor (muOR) mRNA and protein, and regulation of this expression, are of interest.

Regional distribution assessment using a ribonuclease protection assay revealed that the most abundant muOR mRNA was found in thalamus, followed by hypothalamus, midbrain, and spinal cord. This mRNA was also detected in cortex, striatum, brainstem, hippocampus, but not in cerebellum or peripheral tissues. In situ hybridization studies revealed that subpopulations of neurons in several thalamic nuclei express muOR mRNA, with most abundant expression in neurons of the medial aspect of the lateral habenula.

Developmental studies detected muOR mRNA in brains from embryos as early as 14 days gestation. In cerebral cortex, these levels plateaued after birth. In mesencephalon, pons and medulla, however, postnatal development continued to reach expression levels more than 2- fold higher at 6 weeks that at the end of the first week of life. Withdrawal from chronic morphine treatments showed modest effects on rat brain muOR mRNA levels that did not reach statistical significance.

These studies begin to reveal some of the exquisitely detailed regulated expression of this principal receptor for rewarding and analgesic actions of opiate drugs.

Wang J-B, Imai Y, Eppler CM, Gregor P, Spivak C, Uhl GR. mu Opiate receptor/binding protein: cDNA cloning and expression, PNAS 1993;90:10230-4.

Wang JB, Johnson PS, Persico A, Hawkins AL, Griffin CA, Uhl GR. Human mu opiate receptor: cDNA and genomic clones, pharmacologic characterization and chromosomal assignment, FEBS Lett 1994;338:217-22.

Unterwald EM, Rubenfeld JM, Spangler R, Imai Y, Wang JB, Uhl GR and Kreek MJ. Mu opioid receptor mRNA levels following chronic naltrexone administration, Regul Pept 1994;in press.

Schafer M, Imai Y, Uhl GR and Stein C. Peripheral analgesic efficacy of a mu-opioid agonist in relation

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00353-01 MNS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Plasma Membrane Transporter and Vesicular Transporter:: Cloning and Expressing

PRINCIPAL INVESTIGATOR

P.I.	Nobuyuki Takahashi, M.D.,	Visiting Fellow	Molecular Neurobiology Branch
	Stephen Davis, Ph.D.	IRTA	Molecular Neurobiology Branch
	Christopher Surratt, Ph.D.	Sr. Staff Fellow	Molecular Neurobiology Branch
	George Uhl, M.D., Ph.D.	Chief	Molecular Neurobiology Branch

COOPERATING UNITS

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.5	10	0.5

CHECK APPROPRIATE BOXES

☐ (A) Human ☐ (b) Human Tissue ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Amphetamine and its derivatives are well-known as sympathomimetic amines that exert profound influences on dopaminergic neurons in the central nervous system. Cos cells expressing the human plasma membrane dopamine transporter and human dopamine decarboxylase have been constructed. The RT-PCR methodology yielded cDNA fragments with high homology to the recently published acetylcholine vesicular transporter and SV2 synaptic vesicle protein, as well as a novel sequence with homology to multi-drug resistance proteins.

Gonzalez AM, Walther D, Pazos A, Uhl GR. Synaptic vesicular monoamine transporter expression: distribution and pharmacologic profile, Mol Brain Res 1994;22:219-26.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00354-01 GS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Allelic Association Studies in Human Substance Abusers

PRINCIPAL INVESTIGATOR

P.I. George Uhl, M.D., Ph.D. Chief Molecular Neurobiology Branch

Antonio Persico, M.D. Visiting Fellow Molecular Neurobiology Branch

COOPERATING UNITS

Ming Tsuang, M.D., Harvard Medical School

Stephen Goldberg, Ph.D. Preclinical Pharm. Lab

LAB/BRANCH

Molecular Neurobiology Branch

SECTION

Molecular Neurobiology

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.15	0.3	0.75

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☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK

There are large individual differences among humans and animals in behavioral, physiological and toxicological responses to drugs of abuse. Individual differences in human behavioral responses to drugs appear to display substantial genetic influences, although these influences may be provided by several genes. Family studies suggest several severe limitations to pedigree-based likage approaches in drug abuse, suggesting that association studies might be more fruitful. Use of allelic association approaches also mandated careful examination of ethnic differences in populations and linkage disequilibrium at specific loci that can confound these approaches.

Association studies with polymorphic markers at several different dopaminergic gene loci can test the hypothesis that interindividual differences in genes of dopaminergic neurotransmission could contribute to interindividual differences in vulnerability to substance abuse. During this fiscal year, this laboratory has continued to work to develop methods that would allow more sensitive detection of means wherey genes with allelic variants predisposing to substance abuse vulnerability could be identified. This work was accompanied by continuing work on possible confounding features, including racial and ethnic differences in marker frequencies, found in association studies.

Studies of RFLP polymorphic markers at the mu opiate receptor locus failed to reveal allelic association in a number of the same research subjects. However, the association noted between substance abusers and higher frequencies of the TaqI A "allele" of the dopamine D2 receptor was found to be largely due to individuals who had access to drugs in several drug classes, but who preferred cocaine to opiates.

O'Hara BF, Smith SS, Bird G, Persico AM, Suarez B, Cutting GR, Uhl GR. Dopamine D2 Receptor RFLPs haplotypes and their association with substance use in black and caucasian research volunteers, Hum Hered 1993;43:209-18.

Persico AM, O'Hara BF, Farmer S, Gysin R, Flanagan SD, Uhl GR. Dopamine D2 receptor gene Taq 1 'A' locus map including 'A4' variant: relevance for alcoholism and drug abuse, Drug Alcohol Depend 1993;31:229-34.

Uhl G, Blum K, Noble E, Smith S. Substance abuse vulnerability and D2 receptor genes, TINS 1993;16(3):83-8.

Gregor P, O'Hara BF, Yang X, Uhl GR. Expression and novel subunit isoforms of glutamate receptor genes GluR5 and GluR6, NeuroReport 1993;4:1343-6.

Persico AM, Smith SS, Uhl GR. D2 receptor gene variants and substance abuse liability, Seminars in the Neurosciences 1993;5:377-82.

Persico AM, Vandenbergh DJ, Smith SS, Uhl GR. Dopamine transporter gene polymorphisms are not associated with polysubstance abuse, Biol Psychiatry 1993;34(4):265-7.

Smith SS, Newman JP, Evans A, Pickens R, Wydeven J, Uhl GR, Newlin DB. Comorbid psychopathy is not associated with increased D2 dopamine receptor TaqI A or B gene marker frequencies in incarcerated substance abusers, Biol Psychol 1993;33(11-12):845-8.

Lossie AC, Vandenbergh DJ, Uhl GR, Camper SA. Localization of the dopamine transporter gene, Dat1, on mouse chromosome 13, Mammalian Genome 1994;5(2):117-8.

Uhl GR. Association strategies in substance abuse. In: Jansson B, Jornvall H, Rydberg U, Terenius L, Vallee BL, eds. Proceedings of the 86th nobel symposium towards a molecular basis of alcohol use and abuse. Switzerland: Birkhauser Verlag Basel, 1994;133-141.

Uhl GR, Persico A. Meeting Report: Collaborative Approaches in Drug Abuse Genetics, Drug Alcohol Depend 1994;34:161-2.

Reply, Uhl GR: D2 receptor genes - the cause or consequence of substance abuse? Trends in Neurosciences 1994;17(2):50-1.

O'Hara BF, Donovan DM, Lindberg I, Brannock MT, Ricker DD, Moffatt CA, Klaunberg BA, Schindler C, Chang TSK, Nelson RJ, Uhl GR. Proenkephalin transgenic mice: a short promoter confers high testis expression and reduced fertility, Mol Reprod Dev 1994;38:275-84.

Persico AM, Wang ZW, Black DW, Andreasen NC, Uhl GR, Crowe RR. Dopamine transporter gene: exclusion of close linkage with schizophrenia spectrum disorders, Amer J Psych 1994;in press.

Gregor P, Gaston SM, Yang X, O'Regan JP, Rosen DR, Tanzi RE, Patterson D, Haines JL, Horvitz HR, Uhl GR, Brown RH, Jr. Genetic and physical mapping of the GLUR5 glutamate receptor gene on human chromosome 21, Hum Genet 1994;in press.

Uhl GR, Elmer G, LaBuda MC, Pickens R. Genetic influences in drug abuse. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press, 1994;in press.

Persico AM, Wang ZW, Black DW, Andreasen NC, Uhl GR, Crowe RR. Dopamine transporter gene: exclusion of close linkage with schizophrenia spectrum disorders, Amer J Psych 1994;in press.

Uhl GR. Molecular and genetic studies of the targets of acute drug action, substrates for interindividual differences in vulnerability to substance abuse, and candidate mechanisms for addiction. In: Molecular approaches to drug abuse research: Rockville, MD: Dept. of Health and Human Services, National Institute on

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00355-01 BDS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Smoked Drugs: Mechanisms of Reinforcement

PRINCIPAL INVESTIGATOR

P.I.	Jack Henningfield	Chief	Clinical Pharmacology Branch
	Stephen Heishman	Research Psychologist	Clinical Pharmacology Branch
	Wallace Pickworth	Research Pharmacologist	Clinical Pharmacology Branch
	Robert Keenan	Guest Scientist	Clinical Pharmacology Branch
	Leslie Schuh	IRTA	Clinical Pharmacology Branch
	Suzette Evans	Guest Scientist	Clinical Pharmacology Branch

COOPERATING UNITS

Chemistry and Drug Metabolism Section

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1	1	0

CHECK APPROPRIATE BOXES

☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The route of drug administration is itself a determinant of the toxicity and addictiveness of a given drug. The smoked route results in far greater morbidity and mortality than all other forms of drug abuse combined with an excess of 400,000 tobacco caused deaths per year, and increasing numbers of deaths caused directly or indirectly by the smoking of heroin, cocaine, marijuana, and methamphetamine (this includes deaths due to HIV infection which is highly prevalent amount drug smokers due to the strong association of this route with sexual activities). Differences in behavioral and physiologic effects of smoked drugs have been the source of considerable speculation as they pertain to developing more effective treatment and prevention strategies. Unfortunately, the pharmacological effects, including mechanisms of reinforcement, have not received thorough study. In part, this is because there have been technical barriers to conducting quantitative research such as well controlled dosing procedures and rapid methods of assessing behavioral and physiologic responses. Research over the past decade at the ARC and in NIDA extramural laboratories has addressed these issues and provided methods that are now being adapted to a range of scientific questions concerning the pharmacology of smoked drugs.

Over the past year, cocaine, heroin, and nicotine, have been tested, and previously collected data from studies involving both the intravenous and smoked routes of administration (smoked marijuana has also been studied but is reported separately) has undergone analysis. These studies have examined the arterial drug boli produced by smoking cocaine and nicotine to determine if the smoked route provides physiologically more addicting doses than other routes. A study of intravenous nicotine examined the role of rate of drug delivery itself as a possible contributor to the highly addictive nature of drug smoking; this study varied the infusion time of standard doses from 15 to 300 seconds.

Henningfield, J.E. and Keenan, R.M. Nicotine delivery kinetics and abuse liability. Journal of Consulting & Clinical Psycnology, 61(5): 743-750, 1993.

Heishman, S.J., Snyder, F.R. and Henningfield. J.E. Performance, subjective, and physiological effects of nicotine in non-smokers. Drugs and Alcohol Dependence, 34: 11-18, 1993.

Woodson, P.P., Fagerstrom, K.O., Moland, L., Slade, J., and Henningfield, J.E. Premier: A new nicotine delivery system - studies on its environmental and biological impact. Journal of Smoking-Related Disorders, 4(3): 191-201, 1993.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00356-01 BDS

PERIOD COVERED

October 1 1993 to September 30 1994

TITLE OF PROJECT

Pharmacologic Mechanisms and Treatment of Nicotine Dependence

PRINCIPAL INVESTIGATOR

P.I.	Jack Henningfield	Chief	Clinical Pharmacology Branch
	Robert Keenan	Guest Scientist	Clinical Pharmacology Branch
	Wallace Pickworth	Research Pharmacologist	Clinical Pharmacology Branch
	Richard Rothman	Chief	Clinical Pharmacology Branch

COOPERATING UNITS

M. Stitzer, K. Schuh, Johns Hopkins University

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence

INSTITUTE AND LOCATION

National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
2	2	0

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☒ (A) Human ☐ (b) Human Tissue ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The prevalence of nicotine dependence, its accompanying health problems, and the difficulty users have in maintaining abstinence combine to make it one of the most problematic abused drugs in our society. These studies were designed to provide a better understanding of the pathophysiology and mechanisms of nicotine dependence as well as to contribute to the development of putative new smoking cessation treatments.

Several nicotine delivery systems have been developed to aid in smoking cessation. Two of these, nicotine polacrilex and nicotine transdermal patches, have been approved for this purpose. However, new systems are being developed, including a nicotine nasal spray and a nicotine vapor inhaler. These systems are notable for having a more rapid delivery rate, a factor that has been associated with greater potential for abuse. Therefore, although developed as aids for smoking cessation, such systems may be abused in their own right. The first study was designed to examine the physiological, subjective and performance effects of various doses of nicotine nasal spray and vapor inhaler compared to a regular cigarette, which served as a standard positive control. This placebo-controlled, double blind, outpatient study will provide needed information about the abuse liability of these products.

Although it is commonly thought that cotinine, the major metabolite of nicotine, has insignificant pharmacologic activity, cotinine has been shown to be behaviorally active in both humans and other animals. Of particular interest is the recent finding that cotinine administration induces subjective changes in abstinent human cigarette smokers. The purpose of the second study is to characterize the pharmacodynamic effects of cotinine in cigarette smokers undergoing periodic abstinence, including symptoms of tobacco withdrawal, mood and subjective state, drug effect, performance, and endocrine effects. This study, which is in progress, will provide valuable information on a neglected aspect of the pharmacology of tobacco dependence. In addition, if cotinine is effective in suppressing withdrawal, a new pharmacologic treatment may be developed, which could save hundreds of thousands of lives each year in the United States.

Jarvik, M.E. and Henningfield, J.E. Pharmacological adjuncts for the treatment of nicotine dependence. In: Orleans, C.T. and Slade, J.D., (eds.) Nicotine Addiction: Principles and Management. New York: Oxford University Press, pp. 245-261, 1993.

Cohen, C., Pickworth, W.B., Bunker, E.B. and Henningfield, J.E. Caffeine antagonizes EEG effects of tobacco withdrawal. Pharmacology Biochemistry & Behavior, 47(4): 919-926, 1994.

Keenan, R.M., Jarvik, M.E. and Henningfield, J.E. Pharmacology of nicotine dependence. In: Miller, N.S. (ed.) Pharmacological Therapies in Drug and Alcohol Disorders, (in press).

Henningfield, J.E. and Singleton, E.G. Managing drug dependence: Psychotherapy or Pharmacotherapy? CNS Drugs, 1(5): 317-322, 1994.

Henningfield, J.E. Do nicotine replacement medications work? A unique standard for nicotine. Addiction, 89(4): 434-436, 1994.

Keenan, R.M., Jarvik, M.E. and Henningfield, J.E. Pharmacologic treatment of nicotine addiction. In: Miller, N. et al (eds.) Principles of Addiction Medicine, (in press).

Schwandt, L.M.,. and Henningfield. J.E. Withdrawal syndrome: Description and treatment, nicotine. In: Jaffe, J.E. et al (eds.) The Encyclopedia of Drugs and Alcohol. Macmillan Publishing (in press).

Schwandt, L.M. and Henningfield. J.E. Pharmacological treatment of cigarette smoking. In: Jaffe, J.H. et al (eds.) The Encyclopedia of Drugs and Alcohol. New York: Macmillan Publishing (in press).

Henningfield. J.E. and Schuh, L.M. Tobacco dependence: Pharmacologic determinants. Journal of Clinical Pharmacology (in press).

Henningfield. J.E. and Heishman, S.J. The addictive role of nicotine in tobacco use. Psychopharmacology (in press).

Henningfield, J.E., Schuh, L.M. and Heishman, S.J. Pharmacological determinants of cigarette smoking. In: Clark PBS, Quik M, Adlkofer FX, Thurau K, editors. Advances in Pharmacological Sciences, Boston: Birkhauser, in press.

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